**Clinical Study Report Appendix 16.1.1**

Drug Substance Sipavibart

Study Code D7000C00001

# Appendix 16.1.1
# Protocol and Protocol Amendments

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| **Clinical Study Protocol** | |
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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Amendment Number: Not applicable

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator
Study Phase: I/III; and placebo (0.9% sodium chloride for injection)

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## Objectives and Endpoints – Part A

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score $\geq 4$)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

## Objectives and Endpoints – Part B

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 1244 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 44 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (4 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. An ESDR will be conducted after Visit 4 (Day 8), and enrollment of the Part A Main Cohort will be initiated if the safety review concludes that it is appropriate to do so. Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when checked at Visit 5 (Day 181). For participants who take part in Part B, the follow up will be 6 months from the open-label administration of AZD5156, and the total duration of involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B Visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety and immunogenicity study, with Part A comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded). Participants from Part A Main Cohort will continue to the single-arm, open-label Part B, where they will receive a dose of AZD5156, approximately 6 months after their first study intervention administration. Participants who join Part B of the study will remain blinded to the study intervention received at Visit 1 in Part A.

**Number of Participants:**

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 4 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

**Intervention Groups and Duration:**

Part A: Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Part A: Main Cohort: single dose of AZD5156 600 mg IM or AZD7442 600 mg IM.

Part B: single open-label dose of AZD5156 600 mg IM.

The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform an early safety data review of the Part A Sentinel Safety Cohort (up to Day 8), prior to the initiation of

the enrollment of the Part A Main Cohort, and to monitor and assess blinded data periodically in the Part A Main Cohort and unblinded AZD5156 data in Part B (given that Part B is open-label administration of AZD5156).

**Statistical Methods**

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit.

*Primary Objectives*

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters

for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will be evaluated in Part A.

Efficacy Endpoints

Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

Characterization of PK

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time. Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

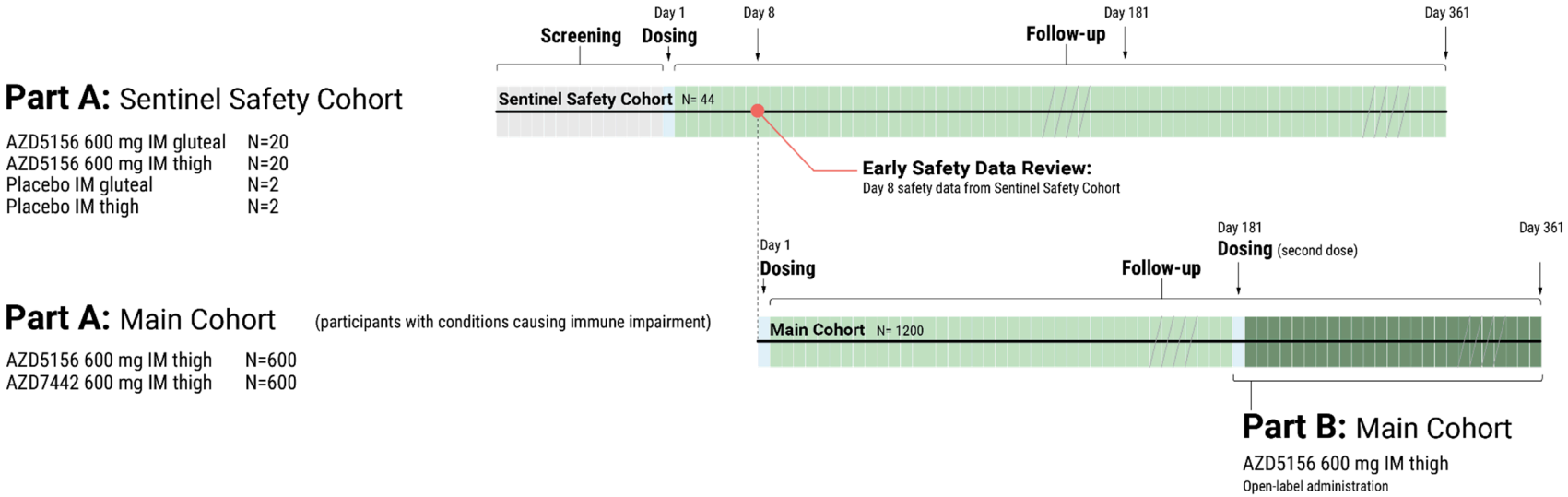
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




IM = intramuscular; N = number of participants.

## 1.3 Schedule of Activities

For Part A Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Part A Main Cohort participants, there will be a treatment and follow-up period lasting 12 months (inclusive of Part B) after administration of study intervention at Visit 1 (Table 3). There will be no separate screening visit for the Part A Main Cohort; screening assessments will be performed at Visit 1, prior to dosing.

All active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will be considered for inclusion in the open-label Part B after approximately 6 months (Table 3).

For Part A Main Cohort and Part B participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| Serum chemistry, hematology, coagulation (local laboratory) | X |
| Urine pregnancy test [a] (WOCBP only) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Pregnancy test must be negative at screening
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | | | | | | | | | | | |
| Vital signs [a] | X (predose) | | | | | | | | | | | X |
| Rapid antigen test for SARS-CoV-2 (performed locally) [b] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | | | | X | | X | | | | | | X |
| Weekly telephone/email/text contacts – monitoring for safety and COVID-19 qualifying symptoms [c] | X ← → | | | | | | | | | | | |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [d] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) [e] | X | | | | | | | | | | | |
| Immediate AEs [f] | X | | | | | | | | | | | |

[a] Any abnormal vital signs must be repeated after the participant has been at rest for at least five minutes. As part of COVID-19 monitoring daily oral temperature measurements during in-house stay and at every outpatient visit will be implemented.

[b] Sites will be provided with rapid antigen tests.
[c] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[d] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[e] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[f] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = antidrug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

### 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| Procedure | Treatment and Follow-up Period | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6[a]** | **7[a]** | **8** | **9** | **EDV** |
| **Day** | **1** | **8** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Written informed consent | X (predose) | | | | | | | | | |
| Informed assent for pediatric participants | X (predose) | | | | | | | | | |
| Verify eligibility criteria | X (predose) | | | | X | | | | | |
| Randomization | X (predose) | | | | | | | | | |
| Medical history and demographics | X (predose) | | | | | | | | | |
| Full physical examination, including height and weight | X (predose) | | | | | | | | | X |
| Vital signs | X [b] | | | | X | | | | | |
| Urine pregnancy test (WOCBP only) [c] | X (predose) | | | | X | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [d] | X (predose) | | | | X | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | X [e] (predose) | | | | X | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6[a]** | **7[a]** | **8** | **9** | **EDV** |
| **Day** | **1** | **8** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [f] | X ← → | | | | | | | | | |
| Assessment of AEs | X | | | | X | | | | | |
| Assessment of SAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | X | X | X | | | | X | X |
| PK serum sample [g] | X (predose) | | X | X | X (predose) | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | | X | X | | | | | | |
| ADA and antidrug nAbs assessment serum sample | X (predose) | | X | X | X (predose) | | X | X | X | X |
| SARS-CoV-2 nAb serum sample | X (predose) | | X | X | X (predose) | | X | X | X | X |
| Exploratory analysis serum sample | X (predose) | | X | X | X (predose) | | X | X | X | X |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| Procedure | Treatment and Follow-up Period | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6[a]** | **7[a]** | **8** | **9** | **EDV** |
| **Day** | **1** | **8** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| **Study intervention administration** | X | | | | X | | | | | |
| Injection site reaction monitoring | X [h] | | | | X [h] | | | | | |
| Immediate AEs [i] | X | | | | X | | | | | |

[a] Participants who do not receive an open-label dose of AZD5156 at Visit 5 will not be required to attend Visits 6 and 7.
[b] Perform predose and again 15 minutes (± 5 minutes) after both injections are complete.
[c] Sample urine test must return a negative result before dosing.
[d] Sites will be provided with rapid antigen tests.
[e] Baseline sample, not a screening sample; results not needed prior to dosing.
[f] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[g] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[h] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[i] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review concludes that it is appropriate to do so.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Saliva sample for viral shedding [d] | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | X | | | | | |
| NP swab SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.
[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.
[d] To be collected when operationally viable.
[e] A local test is required. If an immediate test result is not available, the participant should continue with the Illness Visit schedule until their result has been confirmed. Only if the local laboratory result is unavailable should the central laboratory result be used to assess continuation in Illness Visit schedule.

Note: The Illness Visit schedule is to be performed in addition to the Part A Main Cohort and Part B visit schedules. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

IL-D = illness day; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 22 September 2022, has caused over 610 million confirmed cases of COVID-19, including more than 6.5 million deaths, reported to the WHO (WHO 2022). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein,

which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the currently circulating Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156 has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2

spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE disease. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, and BA.4/5 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

Like AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which formed half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE disease.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE disease is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE disease involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. The disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry, is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the

pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Part A Objectives and Endpoints

**Table 5 Objectives and Endpoints – Part A**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score $\geq 4$)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

Note: Exploratory endpoints may be reported separately from the CSR.

## 3.2 Part B Objectives and Endpoints

**Table 6 Objectives and Endpoints – Part B**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |
| **Exploratory** | |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death during Part B | Incidence of post-treatment symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death |
| Explore additional biomarkers following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data, including exploratory assays for biomarkers thought to play a role in COVID-19 severity or outcomes |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 1244 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 44 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (4 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. An ESDR will be conducted after Visit 4 (Day 8), and enrollment of the Part A Main Cohort will be initiated if the safety review concludes that it is appropriate to do so (for more details on the safety review, see Section 4.1.4). Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when checked at Visit 5 (Day 181). For participants who take part in Part B, the follow up will be 6 months from the open-label administration of AZD5156, and the total duration of involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 4 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single

dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 66 sites from approximately 15 countries.

Adverse events will be collected in the eCRF for 28 days after dosing: up to Visit 6 (Day 29) for Part A Sentinel Safety Cohort participants, Visit 3 (Day 29) for Part A Main Cohort participants, and from Visit 5 (Day 181) to Visit 7 (Day 210) for Part B participants. Serious adverse events and AESIs will be collected throughout the study. The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Part A Sentinel Safety Cohort

The first 44 participants in the study will comprise the Part A Sentinel Safety Cohort. As shown in Table 7, healthy adults 18 to 55 years of age who are enrolled in the Part A Sentinel Safety Cohort will be randomized 10:1 to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Within each group of 22 participants, 20 participants will be randomized to receive AZD5156 and 2 participants will be randomized to receive placebo. Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh).

**Table 7 Description of Part A Sentinel Safety Cohort**

| Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|
| AZD5156 600 mg (20) | Placebo (2) | Gluteal |
| AZD5156 600 mg (20) | Placebo (2) | Anterolateral thigh |

IM = intramuscular; n = number of participants

An ESDR will be performed after the Visit 4 (Day 8) safety data have been collected for the Part A Sentinel Safety Cohort. The safety data collected will be entered into eCRFs and reviewed in an unblinded manner. It is understood that this review is based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDR:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters (if available)

During the ESDR, enrollment of participants will be paused. If the safety review concludes that it is appropriate to continue enrollment of the study, enrollment of the 1200 participants in the Part A Main Cohort will begin as described in the study diagram in Figure 1.

For more details on the ESDR, see Section 4.1.4.

### 4.1.2 Part A Main Cohort

The Part A Main Cohort of the study will enroll approximately 1200 participants 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19 (Table 8). Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Participants must have conditions associated with immune impairment, and thus are most vulnerable to developing severe COVID-19 due to their expected inability to respond adequately to SARS-CoV-2 vaccines, to be eligible for this study. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

**Table 8 Description of Part A Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (600) | AZD7442 600 mg (600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Part A Main Cohort participants are planned to be monitored for approximately 12 months from Visit 1 for safety, PK, and ADA assessments.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Part B

Part A Main Cohort participants will become eligible for joining Part B of the study once they reach Day 181 (+ 4 days) in the Part A Main Cohort (see Section 1.3.3). The dosing interval between Dose 1 (Part A Main Cohort, Day 1) and Dose 2 (Part B, Day 181) will be approximately 6 months. Participants will not need to be reconsented to take part in Part B of the study and will keep the same ID number from Part A. Part B participants will NOT be unblinded from their Part A treatment arm. All participants will receive AZD5156 600 mg IM regardless of original treatment arm in Part A. As with the Part A Main Cohort, AZD5156 will be administered IM in the anterolateral thigh in Part B. Part B participants will be followed for 6 months post the Part B dose, for a total duration in the study of 12 months from Visit 1 of the Part A Main Cohort. Part B participants who develop COVID-19 qualifying symptoms after Visit 5 (Day 181) will be instructed to initiate Illness Visits.

Participants from the Part A Sentinel Safety Cohort will not be eligible for Part B.

### 4.1.4 Safety Review

An ESDR of the Part A Sentinel Safety Cohort's safety data up to Visit 4 (Day 8) will be conducted prior to the initiation of the enrollment of the Part A Main Cohort. The unblinded review will include the AstraZeneca lead physician, the AstraZeneca Patient Safety physician, the AstraZeneca lead study statistician, the AstraZeneca clinical pharmacokineticist, and the AstraZeneca team pharmacometrician who compose the internal Safety Review Committee. Ad hoc members such as an AstraZeneca clinical scientist may be added or consulted on an as-needed basis.

Blinded safety data collected during the conduct of Part A of the study will be analyzed periodically by the Safety Review Committee. Blinded data may also be reviewed in response to AEs assessed as medically-relevant by AstraZeneca or Investigators, and requests to review unblinded data may also be considered if necessary to fully evaluate a potential safety signal. Open-label unblinded safety data collected during the conduct of Part B of the study will also

be analyzed periodically by the Safety Review Committee.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Part A Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Part A Main Cohort and Part B participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses.

### 4.2.2 Rationale for Study Population

The Part A Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Part A Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Part A Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1). Part A Main Cohort participants will also take part in Part B.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as

well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{90}$ for the BA.1, BA.1.1, BA.2, and BA.4/5 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modelled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the

appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Part A Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Part A Sentinel Safety Cohort only if all of the following criteria apply:

1 Age 18 to 55 years at the time of signing the informed consent.
2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
3 Able to attend all scheduled visits and to comply with all study procedures.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Part A Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
2 Known hypersensitivity to any component of the study intervention.
3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.
4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.
5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

11 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

12 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

13 Active infection with hepatitis B or C.

14 Serum creatinine, AST, or ALT above the ULN or hemoglobin, white blood cell count, or platelet count below the lower limit of normal at screening.

15 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

16 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

17 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

18 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

19 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

20 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Part A Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Part A Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Able to attend all scheduled visits and to comply with all study procedures.

4 Negative rapid antigen test at Visit 1.

5 Weight ≥ 40 kg at Visit 1.

6 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have cancer (eg, active solid tumors and hematologic malignancies) except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

7 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

8 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Part A Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

14 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

15 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

16 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 For Part B Participants

### 5.3.1 Inclusion Criteria

Participants from the Part A Main Cohort are eligible to be included in Part B only if all of the following criteria apply:

1 Participant has been randomized into the Part A Main Cohort and is 181 days or more post first dose (Visit 1).
2 The participant must still satisfy at least 1 of the risk factors that were required for inclusion in the Part A Main Cohort (inclusion criterion 6 for the Part A Main Cohort; Section 5.2.1).
3 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease.
4 Documented negative rapid SARS-CoV-2 antigen test at Visit 5 (Day 181) prior to dosing.
5 WOCBP must not be pregnant or lactating, and must still be using a highly effective method of contraception or abstinence until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

### 5.3.2 Exclusion Criteria

Participants are excluded from Part B if any of the following exclusion criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.
2 Known hypersensitivity to any component of the study intervention.
3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.
4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.
5 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.
6 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

7 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

8 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

9 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

10 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.4 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility. Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (10:1 ratio), and in the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). All participants in Part B will receive AZD5156. Details of these study interventions are presented in Table 9.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials. Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Part A Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152; for AZD5156 in the Part A Main Cohort and Part B, label-claim volume per vial is 2 mL for each component; and for AZD7442, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 IM injections, one injection for each component mAb. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material from a single production cell line which will form a Master Cell Bank and constitute the source of the commercial supply. In the Part A Sentinel Safety Cohort, participants will receive only cell pools material. In the Part A Main Cohort, participants will receive only clonal cell material.

The AZD1061 component of AZD5156 will initially be supplied from the AZD7442 clonal cell material for the Part A Sentinel Safety Cohort. A more concentrated formulation for AZD1061 will be administered to participants in the Part A Main Cohort and in Part B.

**Table 9 Investigational Medicinal Products – Part A**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration** | 2 IM injections; 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections of 2 mL each | 2 IM injections of 3 mL each | 2 IM injections of 2 mL each |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

**Table 10 Investigational Medicinal Products – Part B**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152)** |
|---|---|
| **Type** | Drug |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. |
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) |
| **Route of administration** | 2 IM injections of 2 mL each |
| **Use** | Investigational |
| **IMP and NIMP** | IMP |
| **Sourcing** | AstraZeneca |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

## 6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (10:1 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). Part B has an open-label design (all participants will receive AZD5156) and so there will be no randomization required for that cohort.

All participants in the Part A Sentinel Safety Cohort and Part A Main Cohort will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Part A Sentinel Safety Cohort and Part A Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Syringe masking will be required in order to maintain the blind. The Investigator responsible for safety assessment will not attend the study intervention administration session but will be available in case of emergency (eg, anaphylactic shock).

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list
- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)

- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Participants who participate in Part B of the study will not be unblinded for what study intervention they received at Part A Main Cohort Visit 1.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Table 11 lists the permitted and restricted, medications during the study.

**Table 11 Permitted, Restricted, and Prohibited Medications**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening (Part A Sentinel Safety Cohort) or Visit 1 (Part A Main Cohort) and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in Part A will receive a single dose of study intervention (divided into 2 separate doses for each mAb component for AZD5156 or AZD7442). Subjects in Part B will receive a second dose of study intervention (open-label AZD5156 for all Part B participants) approximately 6 months after the first dose. For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance,

or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

### 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Part A Main Cohort and Part B

The study will be put on temporary hold (defined as a pause in enrollment of participants into the Part A Main Cohort and/or dosing of participants in Part B) pending further safety data

analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In the event of a temporary hold for safety reasons, AstraZeneca will carefully review the totality of data, and the risk to all participants will be evaluated by AstraZeneca thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon

occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for Part A Main Cohort/Part B). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, the Omicron variant BA.4/5, and the emerging dominant variant circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) with reminders to monitor for COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week/month. For participants in the Part A Main Cohort and Part B, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must contact the study site.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Part A Main Cohort or after Visit 5 (Day 181) for participants in Part B will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 12).

**Table 12 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Part A Main Cohort or Part B

will be tested locally for SARS-CoV-2 and will be instructed to visit the study site for initiation of illness assessments (Table 4); where supported, home or mobile visits may be substituted for the site visits. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Symptomatic participants will complete IL-D1 and will be instructed to continue with the home collection requirements. Symptomatic participants will continue with the Illness Visits until a laboratory result is available. Only participants who test positive by the local laboratory results will be instructed to continue with the Illness Visits, including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and home laboratory kits. Participants will continue with the main scheduled assessments (ie, Table 2 or Table 3).

Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 in an Illness e-Diary daily.

The Illness Visit schedule is to be performed in addition to the Part A Main Cohort/Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.3).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of virus identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.6.

### 8.2.3 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Part A Sentinel Safety Cohort only (see Section 1.3.1 and Section 1.3.2). Clinical safety laboratory assessments will not routinely be performed for the Part A Main Cohort or during Part B.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 13.

**Table 13 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (Part A Sentinel Safety Cohort), Visit 1 (Part A Main Cohort), or at Visit 5 (Part B). The test must be negative before dosing.

## 8.2.4 Other Safety Assessments

### 8.2.4.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Any AEs should be reported as described in Section 8.3.

#### 8.2.4.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection.

Injection site reactions will be monitored on study days where study intervention is administered. The injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 29 days following administration of study intervention. Any AESIs will be programmatically identified and assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the

eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study

procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be collected according to the time points specified in the SoAs (Section 1.3).

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious. The AESIs will be programmatically identified through AE information that is collected in the eCRF.

The AESIs for AZD5156 and AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically

relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.9.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.10 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.8) and **within 30 days** for all other medication errors.

#### 8.3.10.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 9).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives

immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from

the Part A Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Part A Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated. Serum concentrations of AZD5156 and AZD7442 (and/or component mAbs) will also be evaluated for Part B.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Part A Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for the Part A Main Cohort/Part B). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Antidrug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Part A Main Cohort and Part B only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing

will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

## 9.1 Statistical Hypotheses

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 1244 adults will be randomized in the study. In the Part A Sentinel Safety Cohort, 44 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (4 participants in total). In the Part A Main Cohort, approximately 1200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442. All 1200 participants in the Part A Main Cohort will be considered for inclusion in Part B.

The sample size of 1200 participants in the Part A Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to

provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 14 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Antidrug antibody analysis set | All participants in the FAS with baseline and postdose antidrug antibody result. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints in the Part A Main Cohort and descriptive objectives for Part B.

### 9.4.1 General Considerations

Part A of this study is designed to evaluate AZD5156 compared to AZD7442 for noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and

nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

The analyses of the primary endpoints are described in Section 9.4.3 (SARS-CoV-2 nAb responses) and Section 9.4.5 (safety).

#### 9.4.2.2 Secondary Endpoint(s)

The analysis of the Part A secondary endpoints of SARS-CoV-2 nAb responses against Omicron variant BA.4/5 and the emerging dominant variant circulating during the course of the study is described in Section 9.4.3.

The analysis of the secondary endpoint of AZD5156 and AZD7442 PK is described in Section 9.4.6.

Other secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of post treatment COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death

- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

#### 9.4.2.3 Exploratory Endpoint(s)

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary analysis.

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will also be evaluated in Part A. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Antidrug Antibody Variables

Antidrug antibody variables include status (positive or negative) and titer as follows:

- Total number of participants with negative ADA assay response at all times
- Total number of participants with positive ADA assay response at any time
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay

- Titer values
- Titer category

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

A population PK analysis will be performed for the combined Part A and Part B data and will be reported separately.

## 9.5 Planned Analyses

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit. A total of 2 prespecified analyses are intended. The study will maintain a double-blind period until the primary analysis (ie, blind for participants, Investigators/site staff, and AstraZeneca/designated clinical research organization). To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the Part A treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in an Study

Integrity Plan. Participant-level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented. The final analysis will include data from both study periods, Part A and Part B (open-label administration of AZD5156 at 6 months). The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort (up to Day 8), prior to the initiation of the enrollment of the Part A Main Cohort, and to monitor and assess blinded data periodically in the Part A Main Cohort and unblinded AZD5156 data in Part B (given that Part B is open-label administration of AZD5156), as discussed in Section 4.1.4.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Part A Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the

Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

## D 4 Follow-up

### D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

### D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

(a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

(b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 15, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

| | | |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

| | | |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care

# Appendix F Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Antidrug antibody |
| ADE | Antibody dependent enhanced |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AIDS | Acquired immunodeficiency syndrome |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |

| Abbreviation or special term | Explanation |
|---|---|
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| $IC_{90}$ | Concentration required for 90% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Non-investigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |

| Abbreviation or special term | Explanation |
|---|---|
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

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# SIGNATURE PAGE

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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Amendment Number: 2.0

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator
Study Phase: I/III; and placebo (0.9% sodium chloride for injection)

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 2.0 | 02-Dec-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 2.0 [02 December 2022]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## Objectives and Endpoints – Part A

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

## Objectives and Endpoints – Part B

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 1256 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Part A Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so. Part A Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Part A Main Cohort until Day 15 safety data for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when checked at Visit 5 (Day 181). For participants who take part in Part B, the follow up will be 6 months from the open-label administration of AZD5156, and the total duration of

involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B Visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety and immunogenicity study, with Part A comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded). Participants from Part A Main Cohort will continue to the single-arm, open-label Part B, where they will receive a dose of AZD5156, approximately 6 months after their first study intervention administration. Participants who join Part B of the study will remain blinded to the study intervention received at Visit 1 in Part A.

**Number of Participants:**

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 16 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

**Intervention Groups and Duration:**

Part A: Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Part A: Main Cohort: single dose of AZD5156 600 mg IM or AZD7442 600 mg IM.

Part B: single open-label dose of AZD5156 600 mg IM.

The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b) of the Part A Sentinel Safety Cohort and subsequently prior to enrollment of the Part A Main Cohort.

**Data Safety Monitoring Board:**

The DSMB will meet periodically, review safety data from the Part A Main Cohort and Part B in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. It is understood that these unblinded reviews will be based on preliminary data that will have not been subject to validation and DBL.

**Statistical Methods**

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit.

*Primary Objectives*

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of

GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will be evaluated in Part A.

Efficacy Endpoints

Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

Characterization of PK

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time. Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination

of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

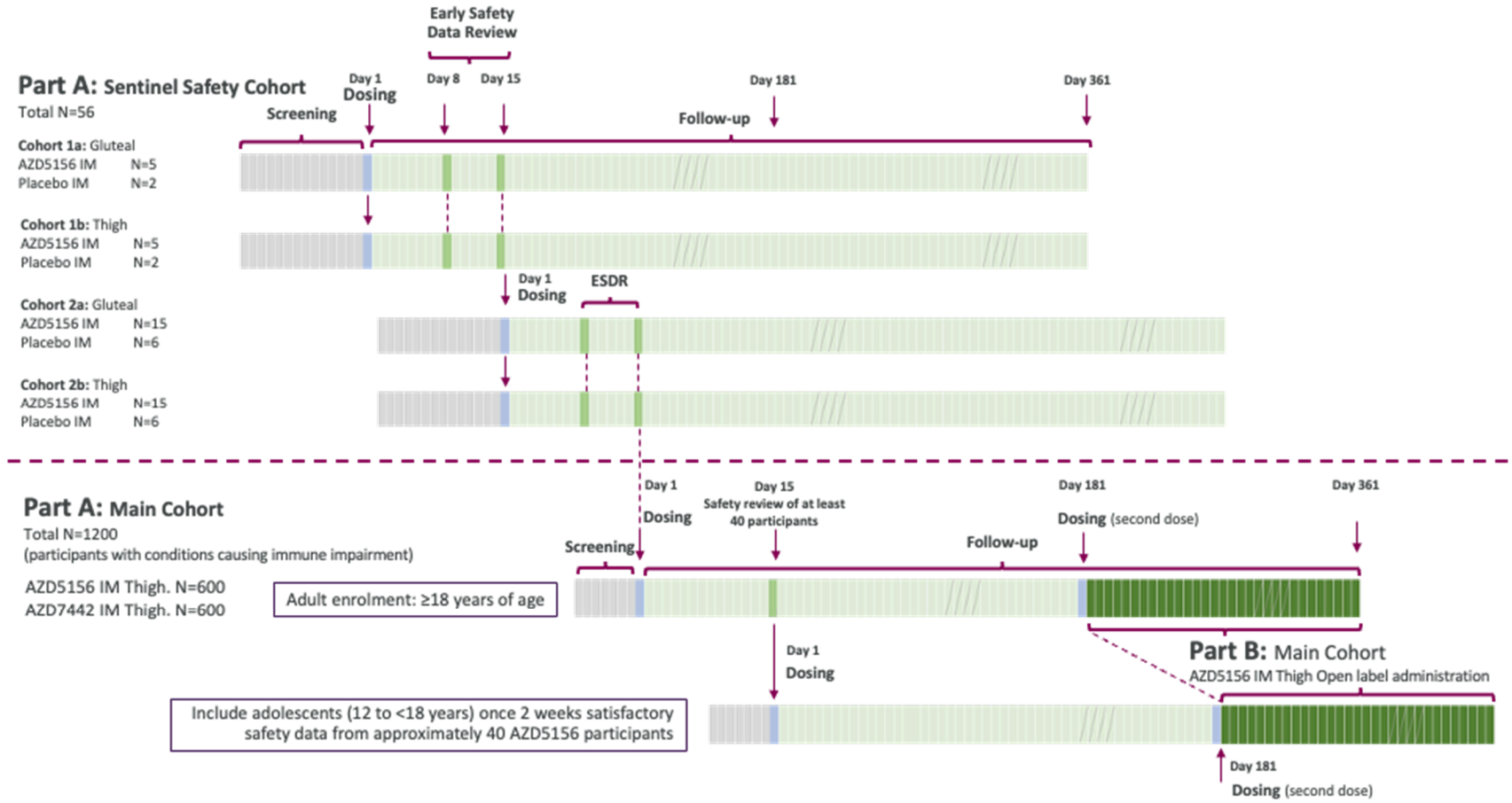
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.
Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort (up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b) and then prior to enrollment of the Part A Main Cohort.
Note: Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed.

## 1.3 Schedule of Activities

For Part A Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Part A Main Cohort participants, there will be a screening period of up to 7 days (Day -7 through Day 1) and a treatment and follow-up period lasting 12 months (inclusive of Part B) after administration of study intervention at Visit 1 (Table 3).

All active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will be considered for inclusion in the open-label Part B after approximately 6 months (Table 3).

For Part A Main Cohort and Part B participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| Electrocardiogram (single, to be performed locally if feasible) | X |
| Serum chemistry, hematology, coagulation (local laboratory) | X |
| Urine pregnancy test [a] (WOCBP only) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Pregnancy test must be negative at screening
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | | | | | | | | | | | |
| Vital signs [a] | X (predose) | | | | | | | | | | | X |
| Rapid antigen test for SARS-CoV-2 (performed locally) [b] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [c] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |
| Assessment of SAEs and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [d] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) [e] | X | | | | | | | | | | | |
| Immediate AEs [f] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.

[b] Sites will be provided with rapid antigen tests.

[c] To be collected at baseline; the results are not needed prior to dosing.

[d] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[e] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[f] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = antidrug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6[b]** | **7[b]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Written informed consent | X | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X (predose) | | | | | |
| Randomization | | X (predose) | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | | | | | | X |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | |
| Vital signs | X | X [c] | | | | | X [c] | | | | | |
| Electrocardiogram (single, to be performed locally if feasible) | X | | | | | | | | | | | |
| Urine pregnancy test (WOCBP only) [d] | X | | | | | | X (predose) | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6[b]** | **7[b]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Rapid antigen test for SARS-CoV-2 (performed locally) [e] | | X (predose) | | | | | X (predose) | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [f] (predose) | | | | | X [f] | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [g] | | X ← → | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | |
| Assessment of SAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | X |
| PK serum sample [h] | | X (predose) | | | X | X | X (predose) | X | X | X | X | X |
| PK nasal lining fluid sample | | X (predose) | | | X | X | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6[b]** | **7[b]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| **Study intervention administration** | | X | | | | | X | | | | | |
| Injection site reaction monitoring | | X [i] | | | | | X [i] | | | | | |
| Immediate AEs [j] | | X | | | | | X | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Participants who do not receive an open-label dose of AZD5156 at Visit 5 will not be required to attend Visits 6 and 7.
[c] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[d] Sample urine test must return a negative result before dosing.
[e] Sites will be provided with rapid antigen tests.
[f] To be collected at baseline. The results are not needed prior to dosing.
[g] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[h] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[i] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[j] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that it is appropriate to do so.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Saliva sample for viral shedding [d] | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | X | | | | | |
| NP swab SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.
[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.
[d] To be collected when operationally viable.
[e] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results will not be reported to sites.

Note: The Illness Visit schedule is to be performed in addition to the Part A Main Cohort and Part B visit schedules. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

IL-D = illness day; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 22 September 2022, has caused over 610 million confirmed cases of COVID-19, including more than 6.5 million deaths, reported to the WHO (WHO 2022). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein,

which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the currently circulating Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156 has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2

spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE disease. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, and BA.4/5 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

Like AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which formed half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE disease.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE disease is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE disease involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. The disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry, is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the

pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be monitored in the present study.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Part A Objectives and Endpoints

**Table 5 Objectives and Endpoints – Part A**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score $\geq 4$)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

Note: Exploratory endpoints may be reported separately from the CSR.

## 3.2 Part B Objectives and Endpoints

**Table 6 Objectives and Endpoints – Part B**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |
| **Exploratory** | |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death during Part B | Incidence of post-treatment symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death |
| Explore additional biomarkers following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data, including exploratory assays for biomarkers thought to play a role in COVID-19 severity or outcomes |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 1256 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Part A Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so (for more details on the safety review, see Sections 4.1.1 and 4.1.4). Part A Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Part A Main Cohort until Day 15 safety data for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when

checked at Visit 5 (Day 181). For participants who take part in Part B, the follow up will be 6 months from the open-label administration of AZD5156, and the total duration of involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 16 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 66 sites from approximately 15 countries.

Adverse events will be collected in the eCRF for 28 days after dosing: up to Visit 6 (Day 29) for Part A Sentinel Safety Cohort participants, Visit 3 (Day 29) for Part A Main Cohort participants, and from Visit 5 (Day 181) to Visit 7 (Day 210) for Part B participants. Serious adverse events and AESIs will be collected throughout the study. The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Part A Sentinel Safety Cohort

The first 56 participants in the study will comprise the Part A Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Part A Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Part A Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 7). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio. Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh).

**Table 7 Description of Part A Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants

The ESDR for the Part A Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- An initial ESDR will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDR, enrollment of participants will be paused. If the ESDR concludes that it is appropriate, then enrollment will be permitted to continue and sites will be informed in writing that dosing of the Part A Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- A further ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Part A Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Part A Main Cohort will only be initiated if the ESDR of all of the Part A Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile.

The safety data collected will be entered into eCRFs and reviewed. This review is based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDR:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters (if available)

For more details on the ESDR, see Section 4.1.4.

### 4.1.2 Part A Main Cohort

The Part A Main Cohort of the study will enroll approximately 1200 participants 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19 (Table 8). Dosing in the Part A Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Part A Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156).

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Participants must have conditions associated with immune impairment, and thus are most vulnerable to developing severe COVID-19 due to their expected inability to respond adequately to SARS-CoV-2 vaccines, to be eligible for this study. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

**Table 8 Description of Part A Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (600) | AZD7442 600 mg (600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Part A Main Cohort participants are planned to be monitored for approximately 12 months from Visit 1 for safety, PK, and ADA assessments.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Part B

Part A Main Cohort participants will become eligible for joining Part B of the study once they reach Day 181 (+ 4 days) in the Part A Main Cohort (see Section 1.3.3). The dosing interval between Dose 1 (Part A Main Cohort, Day 1) and Dose 2 (Part B, Day 181) will be approximately 6 months. Participants will not need to be reconsented to take part in Part B of the study and will keep the same ID number from Part A. Part B participants will NOT be unblinded from their Part A treatment arm. All participants will receive AZD5156 600 mg IM regardless of original treatment arm in Part A. As with the Part A Main Cohort, AZD5156 will be administered IM in the anterolateral thigh in Part B. Part B participants will be followed for 6 months post the Part B dose, for a total duration in the study of 12 months from Visit 1 of the Part A Main Cohort. Part B participants who develop COVID-19 qualifying symptoms after Visit 5 (Day 181) will be instructed to initiate Illness Visits.

Participants from the Part A Sentinel Safety Cohort will not be eligible for Part B.

### 4.1.4 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Sections 4.1.1 and 9.6.

The review will include the AstraZeneca lead physician, the AstraZeneca Patient Safety physician, the AstraZeneca lead study statistician, the AstraZeneca clinical pharmacokineticist, and the AstraZeneca team pharmacometrician who compose the internal Safety Review Committee. Ad hoc members such as an AstraZeneca clinical scientist may be added or consulted on an as-needed basis.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of

AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Part A Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Part A Main Cohort and Part B participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses.

### 4.2.2 Rationale for Study Population

The Part A Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Part A Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Part A Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1). Part A Main Cohort participants will also take part in Part B.

The adolescent population of 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase 3 studies. Given the expected safety and PK profile of AZD5156, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD5156 clinical development plan. The adolescent population was approved for EVUSHELD based on the PK extrapolation.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{90}$ for the BA.1, BA.1.1, BA.2, and BA.4/5 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modelled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Part A Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Part A Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Able to attend all scheduled visits and to comply with all study procedures.
5 Negative rapid antigen test at Visit 1.
6 Weight ≥ 45 kg and ≤ 110 kg at screening.
7 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Part A Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
   – Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
      o Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.

- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

– Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

– The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

– All female participants of childbearing potential must have a negative urine pregnancy test result at screening.

– Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

11 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

12 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

13 Active infection with hepatitis B or C.

14 Serum creatinine, AST, or ALT above the ULN or hemoglobin, white blood cell count, or platelet count below the lower limit of normal at screening.

15 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

16 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

17 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

18 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

19 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

20 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Part A Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Part A Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their

parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Able to attend all scheduled visits and to comply with all study procedures.

4 Negative rapid antigen test at Visit 1.

5 Weight ≥ 40 kg at Visit 1.

6 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have cancer (eg, active solid tumors and hematologic malignancies) except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

7 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

8 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Part A Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion,

intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

14 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

15 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

16 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 For Part B Participants

### 5.3.1 Inclusion Criteria

Participants from the Part A Main Cohort are eligible to be included in Part B only if all of the following criteria apply:

1 Participant has been randomized into the Part A Main Cohort and is 181 days or more post first dose (Visit 1).

2 The participant must still satisfy at least 1 of the risk factors that were required for inclusion in the Part A Main Cohort (inclusion criterion 6 for the Part A Main Cohort; Section 5.2.1).

3 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease.

4 Documented negative rapid SARS-CoV-2 antigen test at Visit 5 (Day 181) prior to dosing.

5 WOCBP must not be pregnant or lactating, and must still be using a highly effective method of contraception or abstinence until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

### 5.3.2 Exclusion Criteria

Participants are excluded from Part B if any of the following exclusion criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined

below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

6 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

7 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

8 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

9 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

10 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.4 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility. Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). All participants in Part B will receive AZD5156. Details of these study interventions are presented in Table 9.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials. Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Part A Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152; for AZD5156 in the Part A Main Cohort and Part B, label-claim volume per vial is 2 mL for each component; and for AZD7442, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 IM injections, one injection for each component mAb. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material from a single production cell line which will form a Master Cell Bank and constitute the source of the commercial supply. In the Part A Sentinel Safety Cohort, participants will receive only cell pools material. In the Part A Main Cohort, participants will receive only clonal cell material.

The AZD1061 component of AZD5156 will initially be supplied from the AZD7442 clonal cell material for the Part A Sentinel Safety Cohort. A more concentrated formulation for AZD1061 will be administered to participants in the Part A Main Cohort and in Part B.

**Table 9 Investigational Medicinal Products – Part A**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration** | 2 IM injections; 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections of 2 mL each | 2 IM injections of 3 mL each | 2 IM injections of 2 mL each |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

**Table 10 Investigational Medicinal Products – Part B**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152)** |
|---|---|
| **Type** | Drug |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. |
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) |
| **Route of administration** | 2 IM injections of 2 mL each |
| **Use** | Investigational |
| **IMP and NIMP** | IMP |
| **Sourcing** | AstraZeneca |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

## 6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). Part B has an open-label design (all participants will receive AZD5156) and so there will be no randomization required for that cohort.

All participants in the Part A Sentinel Safety Cohort and Part A Main Cohort will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Part A Sentinel Safety Cohort and Part A Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Syringe masking will be required in order to maintain the blind. The Investigator responsible for safety assessment will not attend the study intervention administration session but will be available in case of emergency (eg, anaphylactic shock).

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list
- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)

- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Participants who participate in Part B of the study will not be unblinded for what study intervention they received at Part A Main Cohort Visit 1.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy.

Table 11 lists the permitted and restricted, medications for Part A Main Cohort and Part B.

**Table 11 Permitted, Restricted, and Prohibited Medications for Part A Main Cohort and Part B**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in Part A will receive a single dose of study intervention (divided into 2 separate doses for each mAb component for AZD5156 or AZD7442). Subjects in Part B will receive a second dose of study intervention (open-label AZD5156 for all Part B participants) approximately 6 months after the first dose. For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance,

or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 or Section 7.2.2 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any two Grade 3 or higher AEs, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will

be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Part A Main Cohort and Part B

The study will be put on temporary hold (defined as a pause in enrollment of participants into the Part A Main Cohort and/or dosing of participants in Part B) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for Part A Main Cohort/Part B). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, the Omicron variant BA.4/5, and the emerging dominant variant circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) with reminders to monitor for COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week/month. For

participants in the Part A Main Cohort and Part B, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must contact the study site.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Part A Main Cohort or after Visit 5 (Day 181) for participants in Part B will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 12).

**Table 12 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Part A Main Cohort or Part B will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home may be substituted for the site visits. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the

participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 2 or Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in an Illness e-Diary. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

The Illness Visit schedule is to be performed in addition to the Part A Main Cohort/Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.3).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of virus identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as

cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.

- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.6.

### 8.2.3 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Part A Sentinel Safety Cohort only (see Section 1.3.1 and Section 1.3.2). Clinical safety laboratory assessments will not routinely be performed for the Part A Main Cohort or during Part B.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 13.

**Table 13 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts) or at Visit 5 (Main Cohort only). The test must be negative before dosing.

## 8.2.4 Other Safety Assessments

### 8.2.4.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Any AEs should be reported as described in Section 8.3.

#### 8.2.4.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection.

Injection site reactions will be monitored on study days where study intervention is administered. The injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 29 days following administration of study intervention. Any AESIs will be programmatically identified and assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the

eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study

procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be collected according to the time points specified in the SoAs (Section 1.3).

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious. The AESIs will be programmatically identified through AE information that is collected in the eCRF.

The AESIs for AZD5156 and AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically

relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.9.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.10 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.8) and **within 30 days** for all other medication errors.

#### 8.3.10.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 9).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives

immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from

the Part A Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Part A Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated. Serum concentrations of AZD5156 and AZD7442 (and/or component mAbs) will also be evaluated for Part B.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Part A Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$;
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for the Part A Main Cohort/Part B). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Antidrug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Part A Main Cohort and Part B only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing

will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

## 9.1 Statistical Hypotheses

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 1256 adults will be randomized in the study. In the Part A Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Part A Main Cohort, approximately 1200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442. All 1200 participants in the Part A Main Cohort will be considered for inclusion in Part B.

The sample size of 1200 participants in the Part A Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to

provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 14 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Antidrug antibody analysis set | All participants in the FAS with baseline and postdose antidrug antibody result. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints in the Part A Main Cohort and descriptive objectives for Part B.

### 9.4.1 General Considerations

Part A of this study is designed to evaluate AZD5156 compared to AZD7442 for noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and

nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

The analyses of the primary endpoints are described in Section 9.4.3 (SARS-CoV-2 nAb responses) and Section 9.4.5 (safety).

#### 9.4.2.2 Secondary Endpoint(s)

The analysis of the Part A secondary endpoints of SARS-CoV-2 nAb responses against Omicron variant BA.4/5 and the emerging dominant variant circulating during the course of the study is described in Section 9.4.3.

The analysis of the secondary endpoint of AZD5156 and AZD7442 PK is described in Section 9.4.6.

Other secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of post treatment COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death

- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

#### 9.4.2.3 Exploratory Endpoint(s)

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary analysis.

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will also be evaluated in Part A. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Antidrug Antibody Variables

Antidrug antibody variables include status (positive or negative) and titer as follows:

- Total number of participants with negative ADA assay response at all times
- Total number of participants with positive ADA assay response at any time
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay

- Titer values
- Titer category

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

A population PK analysis will be performed for the combined Part A and Part B data and will be reported separately.

## 9.5 Planned Analyses

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit. A total of 2 prespecified analyses are intended. The study will maintain a double-blind period until the primary analysis (ie, blind for participants, Investigators/site staff, and AstraZeneca/designated clinical research organization). To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the Part A treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in an Study

Integrity Plan. Participant-level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented. The final analysis will include data from both study periods, Part A and Part B (open-label administration of AZD5156 at 6 months). The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort, as discussed in Section 4.1.4.

## 9.7 Data Safety Monitoring Board

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Part A Main Cohort and Part B in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. It is understood that these unblinded reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of the first 80 adult participants in Part A Main Cohort (approximately 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Part A Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of

bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Part A Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the

Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

## D 4 Follow-up

### D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

### D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
   (a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   (a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   (b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 15, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

| | | |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

| | | |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care

# Appendix F Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Antidrug antibody |
| ADE | Antibody dependent enhanced |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AIDS | Acquired immunodeficiency syndrome |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |

| Abbreviation or special term | Explanation |
|---|---|
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| $IC_{90}$ | Concentration required for 90% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Non-investigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |

| Abbreviation or special term | Explanation |
|---|---|
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

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# SIGNATURE PAGE

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| Study Intervention | AZD5156 |
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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Amendment Number: 3.0

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator
Study Phase: I/III; and placebo (0.9% sodium chloride for injection)

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 3.0 | 09-Dec-2022 |
| CSP Version 2.0 | 02-Dec-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

## CSP Version 3.0 [09 December 2022]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

## Overall Rationale for the Modification:

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort, at the request of a Regulatory Authority.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination, vital signs, and injection site reaction monitoring (local reactogenicity) have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Sample for clinical safety laboratory assessments added at Day 1 (predose) for the Sentinel Safety Cohort | To obtain baseline values |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For the vital signs assessment on Day 1 of the Sentinel Safety Cohort, the indicator '(predose)' has been deleted | This has been deleted for reasons of clarity, because Day 1 vital signs are not only assessed predose, and the existing footnote (a) provides specific details of the timings |

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## Objectives and Endpoints – Part A

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

## Objectives and Endpoints – Part B

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 1256 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Part A Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so. Part A Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Part A Main Cohort until Day 15 safety data for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when checked at Visit 5 (Day 181). For participants who take part in Part B, the follow up will be 6 months from the open-label administration of AZD5156, and the total duration of

involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B Visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety and immunogenicity study, with Part A comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded). Participants from Part A Main Cohort will continue to the single-arm, open-label Part B, where they will receive a dose of AZD5156, approximately 6 months after their first study intervention administration. Participants who join Part B of the study will remain blinded to the study intervention received at Visit 1 in Part A.

**Number of Participants:**

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 16 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

**Intervention Groups and Duration:**

Part A: Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Part A: Main Cohort: single dose of AZD5156 600 mg IM or AZD7442 600 mg IM.

Part B: single open-label dose of AZD5156 600 mg IM.

The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b) of the Part A Sentinel Safety Cohort and subsequently prior to enrollment of the Part A Main Cohort.

**Data Safety Monitoring Board:**

The DSMB will meet periodically, review safety data from the Part A Main Cohort and Part B in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. It is understood that these unblinded reviews will be based on preliminary data that will have not been subject to validation and DBL.

**Statistical Methods**

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit.

*Primary Objectives*

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of

GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will be evaluated in Part A.

Efficacy Endpoints

Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

Characterization of PK

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time. Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination

of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

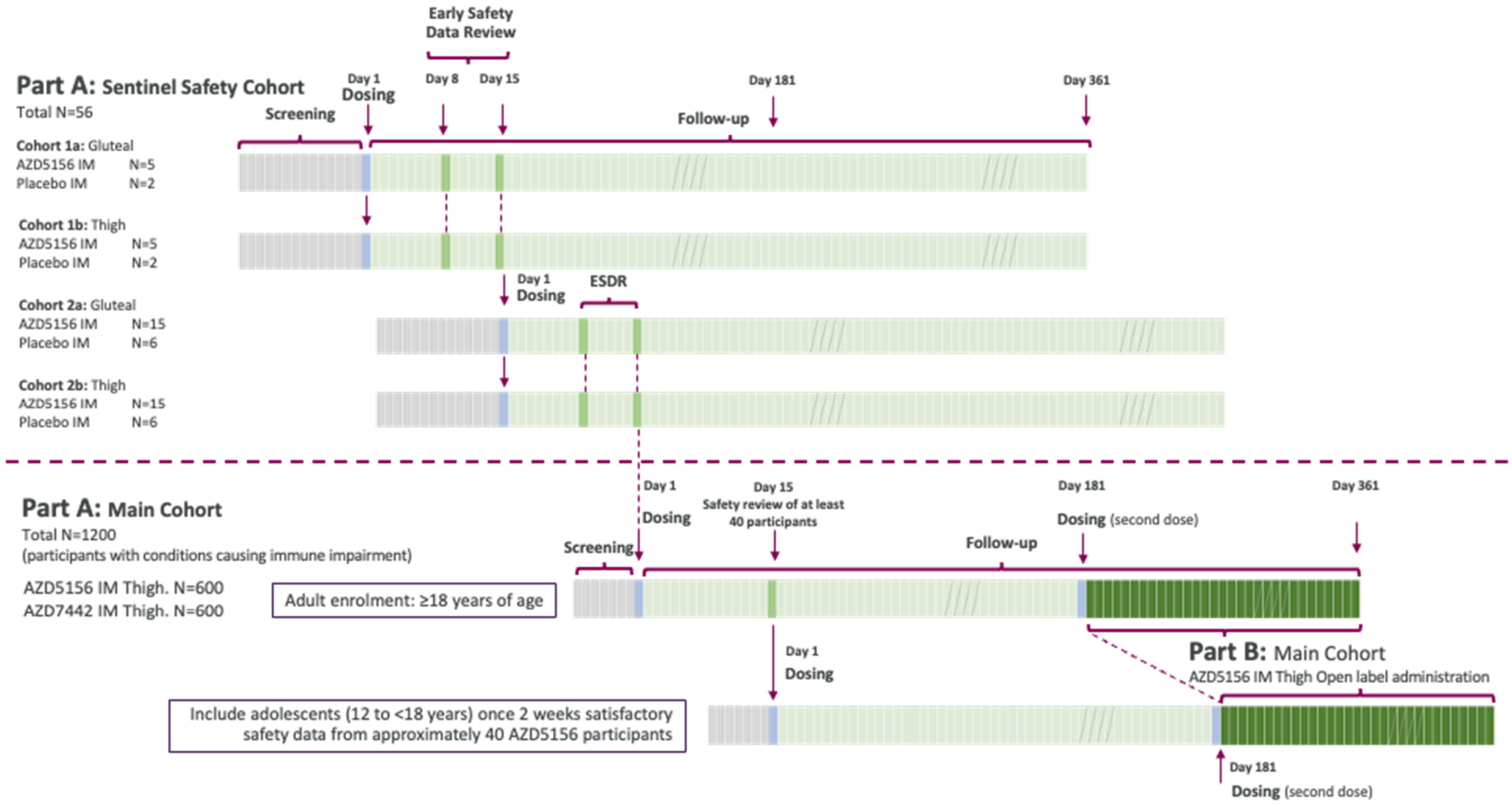
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.
Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort (up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b) and then prior to enrollment of the Part A Main Cohort.
Note: Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed.

## 1.3 Schedule of Activities

For Part A Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Part A Main Cohort participants, there will be a screening period of up to 7 days (Day -7 through Day 1) and a treatment and follow-up period lasting 12 months (inclusive of Part B) after administration of study intervention at Visit 1 (Table 3).

All active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will be considered for inclusion in the open-label Part B after approximately 6 months (Table 3).

For Part A Main Cohort and Part B participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| Electrocardiogram (single, to be performed locally if feasible) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone if applicable for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal

[b] Pregnancy test must be negative at screening

SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Rapid antigen test for SARS-CoV-2 (performed locally) [b] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [c] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |
| Assessment of SAEs and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [d] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [e] | X | X | X | | | | | | | | |
| Immediate AEs [f] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.

[b] Sites will be provided with rapid antigen tests.

[c] To be collected at baseline; the results are not needed prior to dosing.

[d] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[e] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[f] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = antidrug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6[b]** | **7[b]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Written informed consent | X | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X (predose) | | | | | |
| Randomization | | X (predose) | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | | | | | | X |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | |
| Vital signs | X | X [c] | | | | | X [c] | | | | | |
| Electrocardiogram (single, to be performed locally if feasible) | X | | | | | | | | | | | |
| Urine pregnancy test (WOCBP only) [d] | X | | | | | | X (predose) | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6[b]** | **7[b]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Rapid antigen test for SARS-CoV-2 (performed locally) [e] | | X (predose) | | | | | X (predose) | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [f] (predose) | | | | | X [f] | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [g] | | X ← → | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | |
| Assessment of SAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | X |
| PK serum sample [h] | | X (predose) | | | X | X | X (predose) | X | X | X | X | X |
| PK nasal lining fluid sample | | X (predose) | | | X | X | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6[b]** | **7[b]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| **Study intervention administration** | | X | | | | | X | | | | | |
| Injection site reaction monitoring | | X [i] | | | | | X [i] | | | | | |
| Immediate AEs [j] | | X | | | | | X | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Participants who do not receive an open-label dose of AZD5156 at Visit 5 will not be required to attend Visits 6 and 7.
[c] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[d] Sample urine test must return a negative result before dosing.
[e] Sites will be provided with rapid antigen tests.
[f] To be collected at baseline. The results are not needed prior to dosing.
[g] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[h] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[i] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[j] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that it is appropriate to do so.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Saliva sample for viral shedding [d] | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | X | | | | | |
| NP swab SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.
[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.
[d] To be collected when operationally viable.
[e] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results will not be reported to sites.

Note: The Illness Visit schedule is to be performed in addition to the Part A Main Cohort and Part B visit schedules. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

IL-D = illness day; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 22 September 2022, has caused over 610 million confirmed cases of COVID-19, including more than 6.5 million deaths, reported to the WHO (WHO 2022). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein,

which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the currently circulating Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156 has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2

spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE disease. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, and BA.4/5 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

Like AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which formed half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE disease.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE disease is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE disease involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. The disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry, is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the

pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be monitored in the present study.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Part A Objectives and Endpoints

**Table 5 Objectives and Endpoints – Part A**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score $\geq 4$)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

Note: Exploratory endpoints may be reported separately from the CSR.

## 3.2 Part B Objectives and Endpoints

**Table 6 Objectives and Endpoints – Part B**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |
| **Exploratory** | |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death during Part B | Incidence of post-treatment symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death |
| Explore additional biomarkers following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data, including exploratory assays for biomarkers thought to play a role in COVID-19 severity or outcomes |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 1256 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Part A Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so (for more details on the safety review, see Sections 4.1.1 and 4.1.4). Part A Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Part A Main Cohort until Day 15 safety data for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when

checked at Visit 5 (Day 181). For participants who take part in Part B, the follow up will be 6 months from the open-label administration of AZD5156, and the total duration of involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 16 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 66 sites from approximately 15 countries.

Adverse events will be collected in the eCRF for 28 days after dosing: up to Visit 6 (Day 29) for Part A Sentinel Safety Cohort participants, Visit 3 (Day 29) for Part A Main Cohort participants, and from Visit 5 (Day 181) to Visit 7 (Day 210) for Part B participants. Serious adverse events and AESIs will be collected throughout the study. The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Part A Sentinel Safety Cohort

The first 56 participants in the study will comprise the Part A Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Part A Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Part A Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 7). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio. Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh).

**Table 7 Description of Part A Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants

The ESDR for the Part A Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- An initial ESDR will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDR, enrollment of participants will be paused. If the ESDR concludes that it is appropriate, then enrollment will be permitted to continue and sites will be informed in writing that dosing of the Part A Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- A further ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Part A Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Part A Main Cohort will only be initiated if the ESDR of all of the Part A Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile.

The safety data collected will be entered into eCRFs and reviewed. This review is based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDR:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters (if available)

For more details on the ESDR, see Section 4.1.4.

### 4.1.2 Part A Main Cohort

The Part A Main Cohort of the study will enroll approximately 1200 participants 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19 (Table 8). Dosing in the Part A Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Part A Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156).

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Participants must have conditions associated with immune impairment, and thus are most vulnerable to developing severe COVID-19 due to their expected inability to respond adequately to SARS-CoV-2 vaccines, to be eligible for this study. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

**Table 8 Description of Part A Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (600) | AZD7442 600 mg (600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Part A Main Cohort participants are planned to be monitored for approximately 12 months from Visit 1 for safety, PK, and ADA assessments.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Part B

Part A Main Cohort participants will become eligible for joining Part B of the study once they reach Day 181 (+ 4 days) in the Part A Main Cohort (see Section 1.3.3). The dosing interval between Dose 1 (Part A Main Cohort, Day 1) and Dose 2 (Part B, Day 181) will be approximately 6 months. Participants will not need to be reconsented to take part in Part B of the study and will keep the same ID number from Part A. Part B participants will NOT be unblinded from their Part A treatment arm. All participants will receive AZD5156 600 mg IM regardless of original treatment arm in Part A. As with the Part A Main Cohort, AZD5156 will be administered IM in the anterolateral thigh in Part B. Part B participants will be followed for 6 months post the Part B dose, for a total duration in the study of 12 months from Visit 1 of the Part A Main Cohort. Part B participants who develop COVID-19 qualifying symptoms after Visit 5 (Day 181) will be instructed to initiate Illness Visits.

Participants from the Part A Sentinel Safety Cohort will not be eligible for Part B.

### 4.1.4 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Sections 4.1.1 and 9.6.

The review will include the AstraZeneca lead physician, the AstraZeneca Patient Safety physician, the AstraZeneca lead study statistician, the AstraZeneca clinical pharmacokineticist, and the AstraZeneca team pharmacometrician who compose the internal Safety Review Committee. Ad hoc members such as an AstraZeneca clinical scientist may be added or consulted on an as-needed basis.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of

AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Part A Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Part A Main Cohort and Part B participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses.

### 4.2.2 Rationale for Study Population

The Part A Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Part A Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Part A Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1). Part A Main Cohort participants will also take part in Part B.

The adolescent population of 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase 3 studies. Given the expected safety and PK profile of AZD5156, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD5156 clinical development plan. The adolescent population was approved for EVUSHELD based on the PK extrapolation.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{90}$ for the BA.1, BA.1.1, BA.2, and BA.4/5 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modelled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Part A Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Part A Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Able to attend all scheduled visits and to comply with all study procedures.
5 Negative rapid antigen test at Visit 1.
6 Weight ≥ 45 kg and ≤ 110 kg at screening.
7 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Part A Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
   – Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
      o Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.

- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

– Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

– The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

– All female participants of childbearing potential must have a negative urine pregnancy test result at screening.

– Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

11 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

12 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

13 Active infection with hepatitis B or C.

14 Serum creatinine, AST, or ALT above the ULN or hemoglobin, white blood cell count, or platelet count below the lower limit of normal at screening.

15 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

16 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

17 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

18 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

19 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

20 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Part A Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Part A Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their

parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Able to attend all scheduled visits and to comply with all study procedures.

4 Negative rapid antigen test at Visit 1.

5 Weight ≥ 40 kg at Visit 1.

6 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have cancer (eg, active solid tumors and hematologic malignancies) except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

7 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

8 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Part A Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion,

intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

14 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

15 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

16 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 For Part B Participants

### 5.3.1 Inclusion Criteria

Participants from the Part A Main Cohort are eligible to be included in Part B only if all of the following criteria apply:

1 Participant has been randomized into the Part A Main Cohort and is 181 days or more post first dose (Visit 1).

2 The participant must still satisfy at least 1 of the risk factors that were required for inclusion in the Part A Main Cohort (inclusion criterion 6 for the Part A Main Cohort; Section 5.2.1).

3 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease.

4 Documented negative rapid SARS-CoV-2 antigen test at Visit 5 (Day 181) prior to dosing.

5 WOCBP must not be pregnant or lactating, and must still be using a highly effective method of contraception or abstinence until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

### 5.3.2 Exclusion Criteria

Participants are excluded from Part B if any of the following exclusion criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined

below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

6 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

7 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

8 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

9 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

10 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.4 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility. Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). All participants in Part B will receive AZD5156. Details of these study interventions are presented in Table 9.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials. Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Part A Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152; for AZD5156 in the Part A Main Cohort and Part B, label-claim volume per vial is 2 mL for each component; and for AZD7442, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 IM injections, one injection for each component mAb. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material from a single production cell line which will form a Master Cell Bank and constitute the source of the commercial supply. In the Part A Sentinel Safety Cohort, participants will receive only cell pools material. In the Part A Main Cohort, participants will receive only clonal cell material.

The AZD1061 component of AZD5156 will initially be supplied from the AZD7442 clonal cell material for the Part A Sentinel Safety Cohort. A more concentrated formulation for AZD1061 will be administered to participants in the Part A Main Cohort and in Part B.

**Table 9 Investigational Medicinal Products – Part A**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration** | 2 IM injections; 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections of 2 mL each | 2 IM injections of 3 mL each | 2 IM injections of 2 mL each |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

**Table 10 Investigational Medicinal Products – Part B**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152)** |
|---|---|
| **Type** | Drug |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. |
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) |
| **Route of administration** | 2 IM injections of 2 mL each |
| **Use** | Investigational |
| **IMP and NIMP** | IMP |
| **Sourcing** | AstraZeneca |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

## 6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). Part B has an open-label design (all participants will receive AZD5156) and so there will be no randomization required for that cohort.

All participants in the Part A Sentinel Safety Cohort and Part A Main Cohort will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Part A Sentinel Safety Cohort and Part A Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Syringe masking will be required in order to maintain the blind. The Investigator responsible for safety assessment will not attend the study intervention administration session but will be available in case of emergency (eg, anaphylactic shock).

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list
- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)

- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Participants who participate in Part B of the study will not be unblinded for what study intervention they received at Part A Main Cohort Visit 1.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy.

Table 11 lists the permitted and restricted, medications for Part A Main Cohort and Part B.

**Table 11 Permitted, Restricted, and Prohibited Medications for Part A Main Cohort and Part B**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in Part A will receive a single dose of study intervention (divided into 2 separate doses for each mAb component for AZD5156 or AZD7442). Subjects in Part B will receive a second dose of study intervention (open-label AZD5156 for all Part B participants) approximately 6 months after the first dose. For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance,

or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 or Section 7.2.2 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any two Grade 3 or higher AEs, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will

be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Part A Main Cohort and Part B

The study will be put on temporary hold (defined as a pause in enrollment of participants into the Part A Main Cohort and/or dosing of participants in Part B) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for Part A Main Cohort/Part B). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, the Omicron variant BA.4/5, and the emerging dominant variant circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) with reminders to monitor for COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week/month. For

participants in the Part A Main Cohort and Part B, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must contact the study site.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Part A Main Cohort or after Visit 5 (Day 181) for participants in Part B will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 12).

**Table 12 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Part A Main Cohort or Part B will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home may be substituted for the site visits. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the

participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 2 or Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in an Illness e-Diary. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

The Illness Visit schedule is to be performed in addition to the Part A Main Cohort/Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.3).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of virus identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as

cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.

- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.6.

### 8.2.3 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Part A Sentinel Safety Cohort only (see Section 1.3.1 and Section 1.3.2). Clinical safety laboratory assessments will not routinely be performed for the Part A Main Cohort or during Part B.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 13.

**Table 13 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal

For female participants in the Part A Sentinel Safety Cohort aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts) or at Visit 5 (Main Cohort only). The test must be negative before dosing.

## 8.2.4 Other Safety Assessments

### 8.2.4.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Any AEs should be reported as described in Section 8.3.

#### 8.2.4.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection.

Injection site reactions will be monitored on study days where study intervention is administered. The injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release. For the Sentinel Safety Cohort, injection site reactions will also be monitored on Days 3, 5, and 8.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 29 days following administration of study intervention. Any AESIs will be programmatically identified and assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or

her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be collected according to the time points specified in the SoAs (Section 1.3).

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious. The AESIs will be programmatically identified through AE information that is collected in the eCRF.

The AESIs for AZD5156 and AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs.

Where AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.9.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the

participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.10 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.8) and **within 30 days** for all other medication errors.

#### 8.3.10.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is

specified in this protocol will be considered an overdose (see Table 9).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of

this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Part A Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Part A Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated. Serum concentrations of AZD5156 and AZD7442 (and/or component mAbs) will also be evaluated for Part B.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Part A Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$;

- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for the Part A Main Cohort/Part B). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Antidrug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Part A Main Cohort and Part B only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

## 9.1 Statistical Hypotheses

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 1256 adults will be randomized in the study. In the Part A Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Part A Main Cohort,

approximately 1200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442. All 1200 participants in the Part A Main Cohort will be considered for inclusion in Part B.

The sample size of 1200 participants in the Part A Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 14 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Antidrug antibody analysis set | All participants in the FAS with baseline and postdose antidrug antibody result. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints in the Part A Main Cohort and descriptive objectives for Part B.

### 9.4.1 General Considerations

Part A of this study is designed to evaluate AZD5156 compared to AZD7442 for noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the

denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

The analyses of the primary endpoints are described in Section 9.4.3 (SARS-CoV-2 nAb responses) and Section 9.4.5 (safety).

#### 9.4.2.2 Secondary Endpoint(s)

The analysis of the Part A secondary endpoints of SARS-CoV-2 nAb responses against Omicron variant BA.4/5 and the emerging dominant variant circulating during the course of the study is described in Section 9.4.3.

The analysis of the secondary endpoint of AZD5156 and AZD7442 PK is described in Section 9.4.6.

Other secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of post treatment COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

#### 9.4.2.3 Exploratory Endpoint(s)

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary analysis.

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will also be evaluated in Part A. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Antidrug Antibody Variables

Antidrug antibody variables include status (positive or negative) and titer as follows:

- Total number of participants with negative ADA assay response at all times
- Total number of participants with positive ADA assay response at any time
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay
- Titer values
- Titer category

The ADA variables will be assessed and summarized by number and percentage of

participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

A population PK analysis will be performed for the combined Part A and Part B data and will be reported separately.

## 9.5 Planned Analyses

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit. A total of 2 prespecified analyses are intended. The study will maintain a double-blind period until the primary analysis (ie, blind for participants, Investigators/site staff, and AstraZeneca/designated clinical research organization). To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the Part A treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in an Study Integrity Plan. Participant-level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented. The final analysis will include data from both study periods, Part A and Part B (open-label administration of AZD5156 at 6 months). The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Part A Sentinel Safety Cohort, as discussed in Section 4.1.4.

## 9.7 Data Safety Monitoring Board

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Part A Main Cohort and Part B in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. It is understood that these unblinded reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of the first 80 adult participants in Part A Main Cohort (approximately 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Part A Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Part A Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the

Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

## D 4 Follow-up

### D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

### D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
   (a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   (a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   (b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 15, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

| | | |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

| | | |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care

# Appendix F Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Antidrug antibody |
| ADE | Antibody dependent enhanced |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AIDS | Acquired immunodeficiency syndrome |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |

| Abbreviation or special term | Explanation |
|---|---|
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| $IC_{90}$ | Concentration required for 90% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Non-investigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |

| Abbreviation or special term | Explanation |
|---|---|
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# Appendix G Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 2.0 [02 December 2022]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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| **Clinical Study Protocol** | |
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| Study Intervention | AZD5156 |
| Study Code | D7000C00001 |
| Version | 4.0 |
| Date | 16Jan2023 |

# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version Number: 4.0

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator; and placebo (0.9% sodium chloride for injection)

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Brief Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 4.0 | 16-Jan-2023 |
| CSP Version 3.0 | 09-Dec-2022 |
| CSP Version 2.0 | 02-Dec-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 4.0 [16 January 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended to add efficacy as a secondary endpoint to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the Main Cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy of AZD5156 compared with AZD7442. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

The protocol has also been amended to enhance the safety assessments of the Main Cohort, at the request of a Regulatory Authority.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1; noted that the test must return a negative result before dosing | To align with internal guidance for WOCBP |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Additional assessments of vital signs have been added on Days 8 and 189 of the Main Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Pregnancy test added at Visit 1, with the timing specified as prior to randomization | To align with internal guidance for WOCBP (pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Sample for serum chemistry, hematology, coagulation (local laboratory) will be collected on Days 1, 8, and 29; noted that this assessment is to be performed for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of troponin at screening for the Main Cohort | To increase cardiac safety monitoring |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added the footnote clarifying that home or mobile visits by study staff may substitute for site visits to the Day 1 Illness Visit as well | To ensure sites can perform the Day 1 Illness Visit at home, if needed |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e-Diary and training has been added, along with Investigator site review of e-Diary entry completion | Clarification and for consistency |
| 3 Objectives and Endpoints | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP | For both cohorts, the collection period for AEs has been increased |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | administration (was previously to Day 29) | from 28 to 90 days after each dose of study intervention |
| 3 Objectives and Endpoints | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |
| 3 Objectives and Endpoints | References to dominant variants removed | To make the objectives/endpoints less specific |
| 3 Objectives and Endpoints | nAb responses to variant BA.2 will be evaluated | To include current and emerging variants of concern |
| 3 Objectives and Endpoints | Addition of secondary endpoint related to efficacy | Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case will be evaluated as a secondary endpoint |
| 3 Objectives and Endpoints | For the objective '*To characterize the cellular immune responses to SARS-CoV-2*' the following endpoint has been added: *Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing* | To further characterize the cellular immune response |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated. This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total) |
| 4.1 Overall Design | The collection period for AEs has been increased from 28 to 90 days after each dose of study | To align with global regulatory requirements for AE follow up |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | intervention | |
| 4.1 Overall Design | Noted that MAAEs will be collected throughout the study | Consistent with added safety endpoint |
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #4 has been deleted | Duplication with the original inclusion #7 |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11 (original exclusion #10), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15 (original exclusion #14), hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #3 (original inclusion #4) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on negative rapid antigen test at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #4 (original inclusion #5) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Text regarding participants with cancer in Inclusion #5 (original inclusion #6) has been updated to clarify that those with solid tumor cancer who are included in the study must be on active treatment, excluding the exceptions noted; hematologic malignancy has now been noted as a separate risk factor | This was a Regulatory Authority request |
| 5.2.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12 (original exclusion #11), window for | For broader inclusivity |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | COVID-19 has been reduced from 6 to 3 months | |
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Subsection on stopping rules for Main Cohort removed | Replaced with new section on Study Suspension/Early Termination |
| 7.4 Study Suspension/Early Termination | New section | Added for consistency with wording used in AZD7442 studies |
| 8.2.3 Electrocardiograms | New section | Added to describe procedures for ECG |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted that serum chemistry, hematology, coagulation (local laboratory) assessments will be conducted for at least the first 600 participants in the Main Cohort; deleted text stating that clinical safety laboratory assessments will not routinely be performed for the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted (in Table 11) that troponin assessment will be performed in the Main Cohort at screening | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1.1 Determination of Drug Concentration | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.6.2.1 Assessment of Cell-mediated Immune Responses | New section | For consistency with endpoints section |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.7 Data Safety Monitoring Board – Main Cohort | Added MAAEs to the safety parameters that will be assessed as part of the DSMB review | Consistent with MAAEs having been added as a safety endpoint |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Updated footnote to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 1.3 Schedule of Activities | Updated text describing the duration of treatment and follow-up periods from 12 months to 15 months | To reflect the change to the study design to increase the safety collection time |
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Moved the footnote marker for vital signs assessments from dosing days to the overall row header as abnormal vital signs must be repeated at all scheduled vital signs assessments, and not only on dosing days, after the participant has been at rest for at least 5 minutes | Correction for consistency with vital signs assessments for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The numbers of confirmed cases and deaths due to COVID-19 have been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'currently circulating Omicron variants' has been replaced with 'past Omicron variants' | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Specified that cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies | Clarification that these events will be monitored in other AZD5156 studies in addition to the present study |
| 2.3.2 Benefit Assessment | Noted that similarity of AZD5156 to AZD7442 is in terms of structure and mechanism of action | Clarification |
| 2.3.2 Benefit Assessment | Noted that AZD7442 and AZD5156 may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus | Clarification |
| 3 Objectives and Endpoints | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative RT-PCR at baseline to positive at any time up to 6 and 12 months | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 3 Objectives and Endpoints | Minor change to endpoint describing how exploratory samples may be used to align with change in Section 8.5.2.3 | Clarification |
| 4.1 Overall Design | Added that the safety and neutralizing activity of AZD5156 will be compared with AZD7442 for pre-exposure prophylaxis of | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | COVID-19 and that the study will be conducted globally | |
| 4.1 Overall Design | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.1 Overall Design | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1 Overall Design | Added that immediate AEs will be collected for a 1-hour observation period after study intervention administration | Clarification |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Updated text to provide further information on ESDRs | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.2 Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.2 Scientific Rationale for Study Design | Noted that a dose exploration study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.1 Rationale for Administration Site | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions | To further clarify rationale for the administration site |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the threshold (was $IC_{90}$ now $IC_{80}$) | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.1 Inclusion Criteria (Sentinel) | For inclusion #6, clarified that participant must understand and comply with all study requirements/procedures | Clarification |
| 5.2.1 Inclusion Criteria (Main) | For inclusion #7, clarified that participant must understand and comply with all study requirements/procedures (including those at Illness Visits) | Clarification |
| 5.4 Screen Failures | Criteria for rescreening have been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated in the text and in a footnote to Table 8 | Updated to reflect current information |
| 6.1 Study Intervention(s) Administered | Noted in the text and in a footnote to Table 8 that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive the first component of their assigned intervention will all receive the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Added specific details for placebo | Clarification |
| 6.1 Study Intervention(s) Administered | Noted in Table 8 that L-histidine hydrochloride is monohydrate | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage and administration of IMP | Wording added to provide more comprehensive details of IMP storage and administration |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.1 Randomization | Added text that participants will receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention, and those having access to the randomization list during the study | Clarification |
| 6.3.2 Blinding | Removed text about Investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.5 Concomitant Therapy | Minor update to wording regarding the Concomitant Medication eCRF | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the 'Restricted' section in Table 9 | To ensure the correct patient population is enrolled |
| 8 Study Assessments and Procedures | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 8.1.2 Participant-reported COVID-19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | Extra information added regarding e-Diaries and documentation in the eCRF | Updated for clarity |
| 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments | Added text stating that genotypic sequencing analysis and phenotypic characterization would be of SARS-CoV-2 Spike protein mutations rather than of the virus | Clarification |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment, and noted that any observations will | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | be documented in the participant's medical records | |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 8.2.4 Clinical Safety Laboratory Assessments | Included the option for urea results to be reported as blood urea nitrogen, and for prothrombin time results to be reported as international normalized ratio | Clarification |
| 8.2.5.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.5.2 Injection Site Reactions | Noted that diameters of any redness/swelling may be recorded at site visits | Clarification |
| 8.2.5.2 Injection Site Reactions | Removed references to specific time points for the Sentinel Safety Cohort | Those specific details were not needed because reference is made to the SoAs |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Noted that AESIs will be programmatically identified through AE information that is collected in the eCRF | Clarification |
| 8.3.4 Adverse Events of Special Interest | Minor edits made throughout the section | Updated for clarity |
| 8.3.9 Reporting of Serious Adverse Events | Minor change to wording of statement about reporting of SAEs | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.3.11.1 Timelines | Updated wording for SAEs associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.2.3 Additional Serum Immunogenicity | Minor change to statement regarding how exploratory serum samples may be used | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.3 Populations for Analyses | Updated the definition of the SARS-CoV-2 neutralizing antibody analysis set to remove the text 'with quantifiable SARS-CoV-2 serum titers' | This was a Regulatory Authority request related to the inclusion of participants without quantifiable serum titers but who received investigational product |
| 9.3 Populations for Analyses | Updated the definition of the anti-drug antibody analysis set | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.1 General Considerations | Noted that details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses | Clarification |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.4.2 Efficacy | Deleted reference to 'incidence of post treatment COVID-19' as 'incidence of post treatment symptomatic COVID-19' is already specified | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 9.4.4 Anti-drug Antibody Variables | Text regarding anti-drug antibody variables edited, with a reference added to the SAP | To simplify the text to keep the necessary information and refer to the SAP for further details |
| 9.5 Planned Analyses | Added details of analyses for Sentinel Safety Cohort | Clarification |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | team will remain blinded during primary analysis | |
| 9.5 Planned Analyses | Noted that an evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID 19 be observed prior to the final analysis | Clarification |
| 9.7 Data Safety Monitoring Board – Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore, have not been summarized |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| BSSR | Blinded sample size re-estimation |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |

| Abbreviation or special term | Explanation |
|---|---|
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{80}$ | Concentration required for 80% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |

| Abbreviation or special term | Explanation |
|---|---|
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD5156 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha. The study will also assess efficacy of two doses of AZD5156 compared with two doses of AZD7442 given at a 6-month interval.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the efficacy of AZD5156 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD5156 versus AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the nAb responses to the SARS-CoV-2 Omicron variants BA.2 and/or BA.4/5 and the emerging variants of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD5156 compared with AZD7442 for pre-exposure prophylaxis of COVID-19.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort.

The Sentinel Safety Cohort (Phase I) will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that it is appropriate to do so. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component, with the

second injection administered in the contralateral side (gluteal or thigh, as applicable). For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded to study intervention). Participants from the Main Cohort will receive a second dose of their assigned study intervention, approximately 6 months after their first dose.

**Number of Participants:**

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: 2 doses of AZD5156 600 mg IM or AZD7442 600 mg IM (6-month interval).

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Sentinel Safety Cohort as follows: after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b),

and subsequently after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 subcohorts, prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of the first 80 adult participants (at least 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

**Statistical Methods**

Participants' data will be presented by the dosing regimen received.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

The Sentinel Safety Cohort will be summarized separately from the Main Cohort to support review of safety and PK data. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data only. The remaining two analyses will include all available PK and safety data.

The primary analyses will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants in both cohorts have completed their end-of-study visit.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at

Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

Efficacy Endpoints

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD5156 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented.

Other COVID-19 efficacy endpoints are derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against additional Omicron variants such as BA.2 and/or BA.4/5 and the emerging variants circulating during the course of the study will be evaluated using the geometric mean titer ratio (GMTR) between treatment arms.

Characterization of PK

Following initial dosing with AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

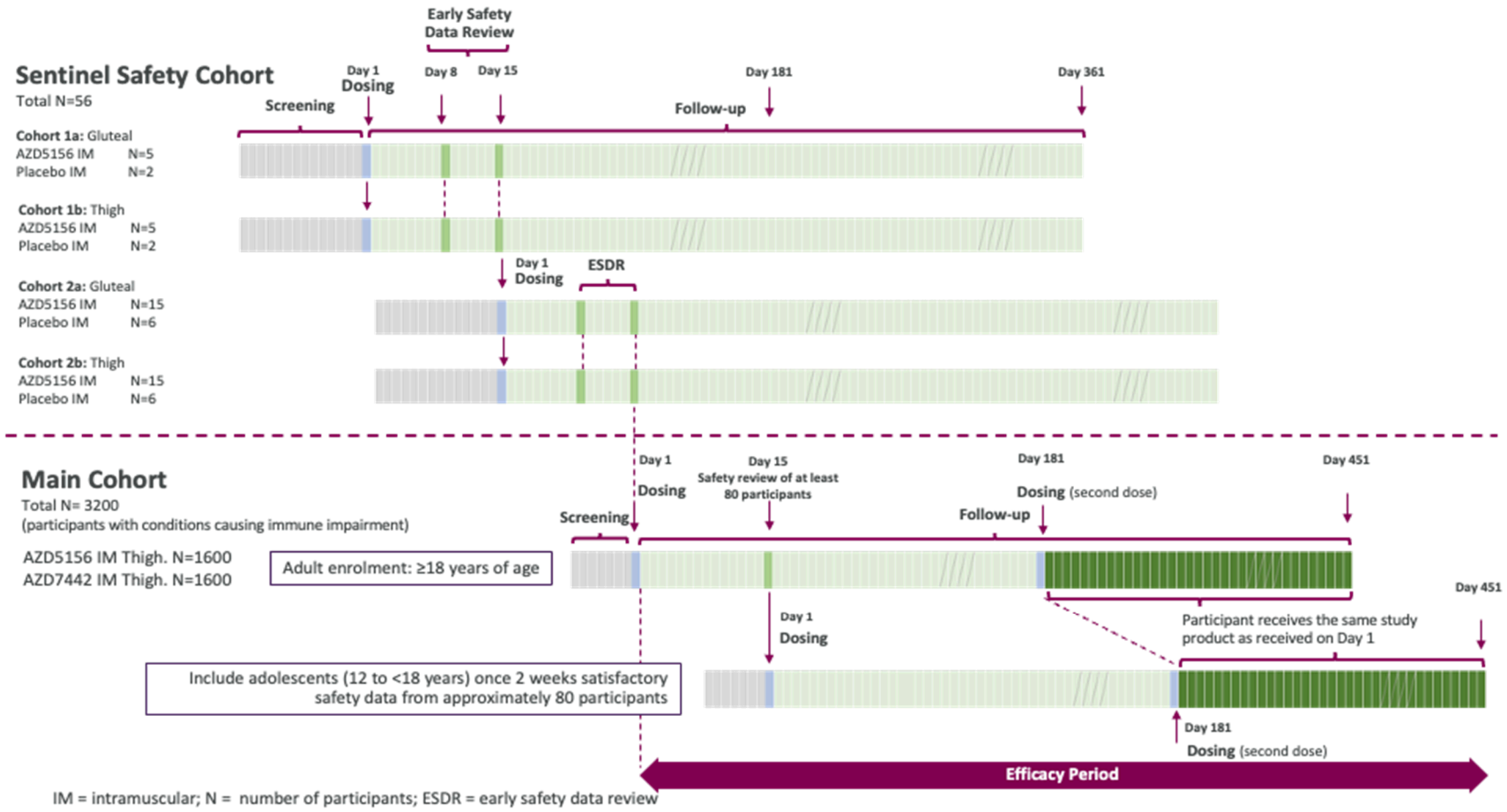
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.
Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort (data up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b), and then prior to enrollment of the Main Cohort.
Note: Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD5156) have been reviewed.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 8 days (Day -7 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| 12-Lead electrocardiogram (single, to be performed locally) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [f] | X | X | X | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | Weight only (predose) | | | | | | X |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [c] | X | X | X | | | | X | X | | | | | |
| 12-lead electrocardiogram (single, to be performed locally) | X | | | | | | | | | | | | |
| Urine pregnancy test (WOCBP only, local laboratory) [d] | X | X (prior to randomization) | | | | | X (predose) | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Rapid antigen test for SARS-CoV-2 (performed locally) [e] | | X (predose) | | | | | X (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [f] (predose) | | | | | X [f] (predose) | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) [g] | | X | X | | X | | | | | | | | |
| Troponin T/I | X | | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [h] | | X ← → | | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |
| PK serum sample [i] | | X (predose) | | | X | X | X (predose) | X | X | X | X | | X |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| PK nasal lining fluid sample [j] | | X (predose) | | | X | X | | | | | | | |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [k] | X | | | | X [k] | X | | | | | |
| Immediate AEs [l] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[d] Sample urine test must return a negative result before dosing. Pregnancy testing prior to each dose is especially important for female participants who had not reached menarche on enrollment into the study.
[e] Sites will be provided with rapid antigen tests.
[f] To be collected at baseline. The results are not needed prior to dosing.
[g] To be performed for at least the first 600 participants in the Main Cohort.
[h] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[i] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.

[j] The nasal lining fluid sample will be collected only for the first 1200 participants (approximately) in the Main Cohort.
[k] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[l] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that it is appropriate to do so.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Set up of e-Diary and training | X | | | | | |
| Assessment of AEs, SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Investigator site review of e-Diary entry completion | X (ongoing) | | | | | |
| Saliva sample for viral shedding | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [d] | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results may not be reported to sites.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.
AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD5156 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha. The study will also assess efficacy of two doses of AZD5156 compared with two doses of AZD7442 given at a 6-month interval.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 11 January 2023, has caused over 660 million confirmed cases of COVID-19, including more than 6.6 million deaths, reported to the WHO (WHO 2023). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the past Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156

has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2 spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, BF.7, XBB, and XBB.1 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is

provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. This is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022). It should be noted that the comparator AZD7442, as well as AZD5156, may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of

AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## Table 5 Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the efficacy of AZD5156 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD5156 versus AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the nAb responses to the SARS-CoV-2 Omicron variants BA.2 and/or BA.4/5 and the emerging variants of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits<br>Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD5156 compared with AZD7442 for pre-exposure prophylaxis of COVID-19. The study will be conducted globally.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort.

The Sentinel Safety Cohort (Phase I) will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that it is appropriate to do so (for more details on the safety review, see Section 4.1.1). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first 56 participants in the study will comprise the Sentinel Safety Cohort. Healthy adults

18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants.

The ESDRs for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- Enrollment will be paused once 14 participants have been recruited in the initial cohorts (1a and 1b). Initial ESDRs will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDRs, enrollment of participants will continue to be paused until after Day 15. If the ESDRs conclude that it is appropriate, then enrollment will be permitted to continue, and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- Enrollment will be paused once more when 42 participants have been recruited into the final 2 cohorts (2a and 2b). Further ESDRs will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile.

The safety data collected will be entered into eCRFs and reviewed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDRs:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD5156).

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (1600) | AZD7442 600 mg (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Section 4.1.1.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021,

Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

A separate dose exploration study (D7000C00004) will be conducted to evaluate the safety, pharmacokinetics, and relative bioavailability of AZD5156.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Main Cohort participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses. The assigned study intervention will be administered as 2 sequential IM injections, one injection for each mAb component, with the second injection administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase III studies. Given the expected safety and PK profile of AZD5156, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD5156 clinical development plan. The adolescent population was

approved for EVUSHELD based on PK extrapolation.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modeled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

### 4.3.3 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals at low risk of development of severe COVID-19 in order to maintain the double-blind in the Sentinel Safety Cohort and to allow objective assessment of the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the AZD7442 Phase I study (D8850C00001).

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an

intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation,

symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN at screening.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test at Visit 1 and Visit 5.

4 Weight ≥ 40 kg at Visit 1 and Visit 5.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have solid tumor cancer and be on active treatment except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have hematologic malignancy
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)

- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

6 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly.

Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure or unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant

according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive only cell pools material. In the Main Cohort, participants at US sites may receive either cell pools material or clonal cell material.

The AZD1061 component of AZD5156 for the Sentinel Safety Cohort will initially be supplied from the AZD7442 clonal cell material, which has a strength of 100 mg/mL. A more concentrated formulation (150 mg/mL) of the clonal cell material for AZD1061 will be administered to participants in the Main Cohort. In the Main Cohort, participants at US sites may receive either the initially supplied AZD7442 material or the more concentrated material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort and the Main Cohort utilizing AZD3152 cell pools material and initially supplied AZD1061 material, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD5156 in the Main Cohort utilizing AZD3152 clonal cell material and the more concentrated AZD1061 formulation, label-claim volume per vial is 2 mL for each component. For AZD7442 in the Main Cohort, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 sequential IM injections, one injection for each component mAb, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895. This will ensure that all participants who only receive the first component of their assigned intervention will all receive the same component (AZD1061).

Placebo for the Sentinel Safety Cohort will be supplied locally by the Sentinel Sites and will also be administered as 2 sequential IM injections, with the second injection administered in the contralateral side (gluteal or thigh, as applicable).

**Table 8 Investigational Medicinal Products**

| Intervention name | AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort and Main Cohort [a] | AZD5156 (AZD1061 + AZD3152) for Main Cohort [a] | AZD7442 (AZD1061 + AZD8895) for Main Cohort | Placebo for Sentinel Safety Cohort |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain either 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain either 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| Intervention name | AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort and Main Cohort [a] | AZD5156 (AZD1061 + AZD3152) for Main Cohort [a] | AZD7442 (AZD1061 + AZD8895) for Main Cohort | Placebo for Sentinel Safety Cohort |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration [b]** | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections (thigh) of 2 mL each | 2 IM injections (thigh) of 3 mL each | 2 IM injections (gluteal or thigh): 3 mL and 2 mL |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive only cell pools material. In the Main Cohort, participants at US sites may receive either cell pools material or clonal cell material.
The AZD1061 component of AZD5156 for the Sentinel Safety Cohort will initially be supplied from the AZD7442 clonal cell material, which has a strength of 100 mg/mL. A more concentrated formulation (150 mg/mL) of the clonal cell material for AZD1061 will be administered to participants in the Main Cohort. In the Main Cohort, participants at US sites may receive either the initially supplied AZD7442 material or the more concentrated material.

[b] The second injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The Investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature-monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156, AZD7442, and placebo for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (ie, the individual

storage time limits are not additive). AZD5156, AZD7442, and placebo do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system

- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives

during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals should not be given within at least 2 weeks prior to Visit 1. Unless the participant develops COVID-19, at which point standard of care treatment is allowed, COVID-19 antivirals should not be given during the study until after the Day 29 assessments. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to each dose of IMP. |

IMP = investigational medicinal product; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD5156 or AZD7442), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose. For each dosing occasion, if a participant experiences an immediate

hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in

participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any two Grade 3 or higher AEs, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the

participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that, in the opinion of the Sponsor, may preclude further administration of IMP.
- If one or more participant experiences a grade IV hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If two or more participants, within the first 300 participants, experience a grade III or higher hypersensitivity reaction.
- If two or more participants, within the first 300 participants, experience a grade III or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with study intervention until the relevant safety review has been conducted.

If the study is suspended or the decision is made not to proceed to the Main Cohort, a protocol amendment will be submitted to Health Authorities.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood

count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, additional Omicron variants such as BA.2 and/or BA.4/5, and the emerging variants circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week. For participants in the Main Cohort, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must be advised to contact the study site as soon as possible.

For participants in the Sentinel Safety Cohort, if SARS-CoV-2 symptoms are reported, an Illness Visit is not required. The participant should be instructed to seek care via their usual healthcare provider.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Main Cohort will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020.

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

At IL-D1, the study site will issue an Illness e-Diary and train the participant on how and when to complete the e-Diary and document their daily symptoms. Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in the Illness e-Diary. The status of ongoing symptoms reported in the e-Diary at the end of an illness series will be recorded. The end date for any symptoms still present after 14 days will be documented in the eCRF. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.4).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of SARS-CoV-2 Spike protein mutations identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the

Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs, and any observations will be documented in the participant's medical records (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Electrocardiograms

A single 12-lead ECGs will be performed at screening (time points specified in the SoA; see Section 1.3). A 12-lead ECG will be obtained after 5 minutes' supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any

abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as unscheduled assessments.

All ECG readings will be digitally stored as source documents.

### 8.2.4 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort (see Section 1.3.1, Section 1.3.2, and Section 1.3.3).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea (or blood urea nitrogen) | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T/I (Main Cohort; screening only) |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) (or international normalized ratio) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal.

For female participants in the Sentinel Safety Cohort aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts), Visit 1 (both cohorts), and Visit 5 (Main Cohort only). The test must be negative before dosing. This is especially important for any female participants who have not reached menarche at enrollment into the study and whose child-bearing potential is expected to change during the study.

### 8.2.5 Other Safety Assessments

#### 8.2.5.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration

to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.5.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling may be recorded in the medical record at site visits.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following administration of study intervention. Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)

- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156 and AZD7442 in this study are based on those identified for EVUSHELD and are as follows:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoAs (Section 1.3).

Medically attended adverse events are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs.

Where AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN occurs, where no other reason,

other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.10.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study

specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites

operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, nasal lining fluid samples will be collected only for the first 1200 participants (approximately). Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$;
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being

screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by

next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

#### 8.6.2.1 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing peripheral blood mononuclear cells using methods that may include flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor. Samples will be collected at Illness Visit time points specified in the SoAs (Section 1.3). Additionally, plasma may be isolated from the whole blood samples collected to isolate peripheral blood mononuclear cells, which can be utilized for exploratory immunogenicity and biomarker analyses.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants' data will be presented by the dosing regimen received.

## 9.1 Statistical Hypotheses

The primary objectives are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442.

A BSSR may be conducted prior to the primary analysis. The overall symptomatic COVID-19 event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed. Full details will be in a BSSR plan.

The sample size in the Main Cohort is driven by the total number of events required to demonstrate the efficacy of AZD5156 versus AZD7442 in the prevention of symptomatic

COVID-19. A minimum of 40 events will provide at least 90% to detect HR of 0.3, or a 70% reduction in hazard. Under the assumption that the event rate will be approximately 3.2% AAR in the AZD7442 arm, HR of 0.30 (70% efficacy), significance level of $\alpha = 0.05$, and 10% attrition. A target sample of approximately 3200 participants has been selected to reach the required number of events assuming participants were observed for 8 months or more. Assumptions are based on data from prior studies with AZD7442 and reported estimates of the AAR among those with immunocompromising conditions (Kelly et al 2022).

A sample size of approximately 1200 participants in the Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

The Main Cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD5156 compared with 1600 participants receiving a US EUA granted and EU MAA approved active comparator, AZD7442 (EVUSHELD).

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Anti-drug antibody analysis set | All participants in the FAS who have a non-missing baseline and at least one non-missing post-baseline anti-drug antibody result. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |
| Immunobridging analysis set | Participants in the FAS who have a baseline and post intervention Day 29 antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

This study is designed to evaluate the immunobridging, efficacy, and safety of AZD5156 compared with AZD7442. The primary endpoint is a noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received. Methods for controlling multiplicity across endpoints will be presented separately in the SAP for the immunobridging and efficacy analyses.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses.

### 9.4.2 Efficacy

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops symptomatic COVID-19 at any time up to Visit 9 (12 months). Positive cases require a central RT-PCR test and meet the qualifying symptoms satisfying the modified WHO definition of symptomatic COVID-19 (see Section 8.1.2).

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD5156 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Participants who become unblinded to treatment assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding or receipt of the first dose of COVID-19 preventive product. Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and will be included in the analysis. Participants who withdraw early from the

study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

Other efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against additional Omicron variants such as BA.2 and/or BA.4/5 and the emerging variants circulating during the course of the study will also be evaluated. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Anti-drug Antibody Variables

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed. Further details are provided in the SAP.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following initial dosing with AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

## 9.5 Planned Analyses

The Sentinel Safety Cohort will be summarized separately from the Main Cohort to support review of safety and PK data. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data only. The remaining two analyses will include all available PK and safety data.

The primary analyses will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants in both cohorts have completed their end-of-study visit. An evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID-19 be observed prior to the final analysis. The study will maintain a double-blind period until the primary analysis. To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan; the study team will remain blinded. Participant-level unblinding information will be kept strictly confidential, and the rationale for any unblinding will be documented. The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and

there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee – Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort, as discussed in Section 4.1.1.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of the first 80 adult participants (at least 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but

are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

## D 4 Follow-up

### D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

### D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
   (a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   (a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   (b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 13, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care.

# Appendix F Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 3.0 [09 December 2022]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort, at the request of a Regulatory Authority.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination, vital signs, and injection site reaction monitoring (local reactogenicity) have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Sample for clinical safety laboratory assessments added at Day 1 (predose) for the Sentinel Safety Cohort | To obtain baseline values |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For the vital signs assessment on Day 1 of the Sentinel Safety Cohort, the indicator '(predose)' has been deleted | This has been deleted for reasons of clarity, because Day 1 vital signs are not only assessed predose, and the existing footnote (a) provides specific details of the timings |

**CSP Version 2.0 [02 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

Note: due to a typing error, the word 'imitating' appears several times instead of 'initiating' in this historical Summary of Changes, and reference is made to the fact that '*no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed*'; this should have read 80 adult Main Cohort participants.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version Number: 5.0

Study Intervention:

*Sentinel Safety Cohort*
AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152), and placebo (0.9% sodium chloride for injection)

*Main Cohort*
AZD3152 monoclonal antibody plus placebo (0.9% sodium chloride for injection) and AZD7442 (EVUSHELD™), the active comparator

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Brief Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 5.0 | 07-Feb-2023 |
| CSP Version 4.0 | 16-Jan-2023 |
| CSP Version 3.0 | 09-Dec-2022 |
| CSP Version 2.0 | 02-Dec-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 5.0 [07 February 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| TITLE PAGE | The study intervention has been changed from 'AZD5156' to 'AZD5156/AZD3152' and a similar change has been made to the study title | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy, although AZD5156 will still be studied in the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of follicle stimulating hormone at screening | Required for eligibility criteria |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples have been removed from Day 271 and the EDV | Rationalization of blood sampling to reduce invasive procedures |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 2.1 Study Rationale | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.3 Benefit/Risk Assessment | Section updated throughout to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and overall benefit/risk conclusion aligned with Investigator's Brochure. | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy; also text aligned with Investigator's Brochure |
| 3 OBJECTIVES AND ENDPOINTS | Created separate primary and secondary objectives and endpoints for the Sentinel Safety and Main Cohorts | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.1 Overall Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.2 Main Cohort | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2 Scientific Rationale for Study Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | New section | Justification as to why AZD7442 is considered a better choice of control than placebo |
| 4.3.2 Justification for AZD3152 Dose | New section | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #10, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #21, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, any alkylating agents will qualify as a risk factor, not just high-dose agents | Low-dose cyclophosphamide is used as immunotherapy in lymphoma, breast and ovarian cancer |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, a moderate or severe secondary immunodeficiency will now qualify as a risk factor | To broaden the study population |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #11, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #13, noted that concurrent participation in another interventional study where the participant ceased IMP treatment >90 days who is in the follow-up period of the study and not expected to receive further IMP is permitted for inclusion | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #17, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.1 Study Intervention(s) Administered | The whole section (including the table) has been updated to reflect the use of AZD3152 as a standalone therapy in the Main Cohort, including use of placebo to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.5 Concomitant Therapy | Added more details regarding permitted concomitant medications for the Sentinel Safety Cohort and clarified the wording around SARS-CoV-2 vaccines and COVID-19 antivirals | Clarification |
| 8.5.1.1 Determination of Drug Concentration | Serum PK samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 8.5.2.1 Anti-drug Antibody Assessments | Samples for determination of ADA will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 9.1 Statistical Hypotheses | The whole section has been updated to reflect the use of AZD3152 as a standalone therapy | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.2 Sample Size Determination | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156; minor adjustments made to wording of sample size determination | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Schema updated in line with applicable changes from the protocol text | Schema made consistent with amended text |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Timing of Day 1 urine pregnancy test changed from 'prior to randomization' to 'predose' and footnote updated to clarify test must be on same day as dosing | Consistency with other parts of the table |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Clarified that laboratory safety samples on Day 1 will be taken predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Noted that duration of recording daily symptoms associated with COVID-19 will be 14 days | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 4.1 Overall Design | Wording regarding qualification for Illness Visits has been updated | Clarification |
| 4.1.1 Sentinel Safety Cohort | Added justification for use of AZD5156 safety data to initiate dosing with AZD3152 in the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.1 Rationale for Administration Site | Removed reference to components of the study interventions being monoclonal antibodies | One injection for those assigned to AZD3152 will be placebo |
| 4.2.2 Rationale for Study Population | Changed references to AZD5156 to AZD3152 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.3.1 Justification for AZD5156 Dose | Noted that AZD5156 will be administered in the Sentinel Safety Cohort | Clarification |
| 4.3.4 Justification for Placebo | Added details of administration of placebo that will be included with AZD3152 to maintain the blind | One injection for those assigned to AZD3152 will be placebo |
| 4.4 End of Study Definition | Noted that results from some laboratory samples may not become available until after the study completion date | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | AZD3152 is now included | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.1 Randomization | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.2 Blinding | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.2 Blinding | Added AstraZeneca Bioanalytical monitor and unblinded Biometric teams to the list of those who will have access to the randomization list during the study | Clarification |
| 7.1 Discontinuation of Study Intervention | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort, also added clarification about process if participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Noted that AstraZeneca will make the final decision on a temporary hold after analysis of the safety data | Clarification |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Clarified that study would be put on temporary hold if Grade 3 or higher AEs were reported for at least 2 participants (and not simply when 2 Grade 3 or higher AEs were reported) | Wording made consistent with previous AZD7442 studies |
| 8.2.2 Vital Signs | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed) | Clarification regarding the time around vital signs collection |
| 8.2.4 Clinical Safety Laboratory Assessments | Removed reference to Laboratory Manual | Not applicable |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that glucose assessment is specifically glucose (random), and added pregnancy test and FSH to the table of variables | Clarification |
| 8.2.4 Clinical Safety Laboratory Assessments | Added clarifications around pregnancy testing. Furthermore, the FSH evaluation no longer applies only to those in the Sentinel Safety Cohort. | Clarification |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Reiterated that SAEs, MAAEs, and AESIs will be collected throughout the study | Clarification |
| 8.3.4 Adverse Events of Special Interest | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.3.9 Reporting of Serious Adverse Events | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.1 Pharmacokinetics | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.2.1 Anti-drug Antibody Assessments | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.6.2 Other Study-Related Biomarker Research | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.1 General Considerations | Description of study updated to reflect change of strategy in terms of using AZD3152 alone | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.2 Efficacy | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.6 Pharmacokinetics | Order of paragraphs reversed, so that Sentinel Safety Cohort is discussed first, text regarding Main Cohort updated to reference AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Removed text regarding an emerging VOC significantly affecting the neutralization activity of AZD7442 | Updated information, as there is a possibility that the situation described in the deleted text may have already occurred |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.7 Data Safety Monitoring Board – Main Cohort | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| BSSR | Blinded sample size re-estimation |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |

| Abbreviation or special term | Explanation |
|---|---|
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{80}$ | Concentration required for 80% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |

| Abbreviation or special term | Explanation |
|---|---|
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD3152 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

D7000C00001 is a Phase I/III study. The Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442] and AZD3152) in healthy adults. The Phase III Main Cohort will assess the safety and neutralizing activity of AZD3152 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19.

This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan, to AZD3152 through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha. The study will also assess efficacy of two doses of AZD3152 compared with two doses of AZD7442 given at a 6-month interval.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD3152 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the efficacy of AZD3152 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus AZD7442) using a hazard regression model. |
| To compare the nAb responses to the SARS-CoV-2 Omicron variants BA.2 and/or BA.4/5 and the emerging variants of concern circulating during the course of the study in serum following AZD3152 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD3152 compared with AZD7442 for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with AZD7442.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are

less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg (to maintain the blind, each administration of AZD3152 in the Main Cohort will comprise of one injection of AZD3152 and one injection of placebo) or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD3152 300 mg plus placebo or AZD7442 600 mg) will be administered as 2 sequential IM injections in the thigh, one injection for each component, with the second injection administered in the contralateral side. For participants assigned to AZD3152, AZD3152 should be administered first followed by placebo. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded to study intervention). Participants from the Main Cohort will receive a second dose of their assigned study intervention, approximately 6 months after their first dose.

**Number of Participants:**

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD3152 (plus placebo) or AZD7442.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: 1 dose of AZD3152 300 mg IM and 1 dose of placebo (to maintain the blind) (on 2 occasions with a 6-month interval) or AZD7442 600 mg IM (on 2 occasions with a 6-month interval).

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Sentinel Safety Cohort as follows: after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b), and subsequently after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 subcohorts, prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

**Statistical Methods**

Participants' data will be presented by the dosing regimen received.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations,

mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

The Sentinel Safety Cohort will be summarized separately from the Main Cohort to support review of safety and PK data. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data only. The remaining two analyses will include all available PK and safety data.

The primary analyses for the Main Cohort will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants in both cohorts have completed their end-of-study visit.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD3152 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD3152 or AZD7442 in the Main Cohort. Separately, safety and PK of AZD5156 will be evaluated in the Sentinel Safety Cohort.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD3152 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

Efficacy Endpoints

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD3152 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented.

Other COVID-19 efficacy endpoints are derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against additional Omicron variants such as BA.2 and/or BA.4/5 and the emerging variants circulating during the course of the study will be evaluated using the geometric mean titer ratio (GMTR) between treatment arms.

Characterization of PK

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of these 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Evaluation of ADA

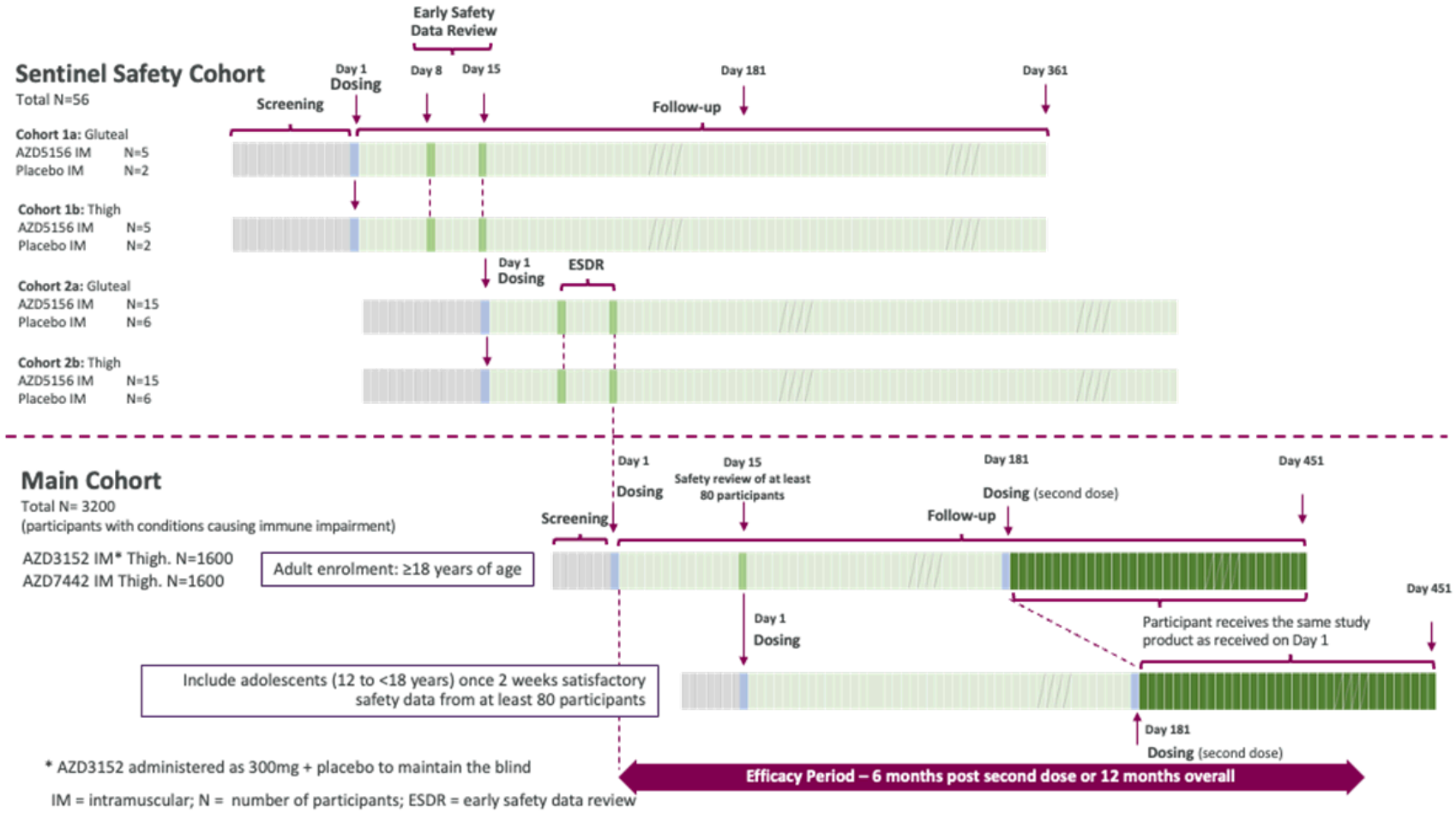
The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and

efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.
Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort (data up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b), and then prior to enrollment of the Main Cohort.
Note: Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 8 days (Day -7 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| 12-Lead electrocardiogram (single, to be performed locally) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [f] | X | X | X | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | Weight only (predose) | | | | | | X |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [c] | X | X | X | | | | X | X | | | | | |
| 12-lead electrocardiogram (single, to be performed locally) | X | | | | | | | | | | | | |
| Urine pregnancy test (WOCBP only, local laboratory) [d] | X | X (predose) | | | | | X (predose) | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Rapid antigen test for SARS-CoV-2 (performed locally) [e] | | X (predose) | | | | | X (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [f] (predose) | | | | | X [f] (predose) | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) [g] | | X (predose) | X | | X | | | | | | | | |
| Troponin T/I | X | | | | | | | | | | | | |
| Follicle stimulating hormone [h] | X | | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [i] | | X ← → | | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |

## Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| PK serum sample [j,k] | | X (predose) | | | X | X | X (predose) | X | X | | X | | |
| PK nasal lining fluid sample [k] | | X (predose) | | | X | X | | | | | | | |
| ADA and antidrug nAbs assessment serum sample [k] | | X (predose) | | | X | X | X (predose) | | X | | X | | |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [l] | X | | | | X [l] | X | | | | | |
| Immediate AEs [m] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[d] Sample urine test must return a negative result before dosing. Pregnancy testing prior to each dose must be on the same day as dosing and is especially important for female participants who had not reached menarche on enrollment into the study.
[e] Sites will be provided with rapid antigen tests.
[f] To be collected at baseline. The results are not needed prior to dosing.
[g] To be performed for at least the first 600 participants in the Main Cohort.

[h] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[i] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[j] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[k] Samples collected only for the first 1200 participants (approximately) in the Main Cohort.
[l] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[m] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Set up of e-Diary and training | X | | | | | |
| Assessment of AEs, SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily for 14 days by participant in Illness e-Diary) | X ← → | | | | | |
| Investigator site review of e-Diary entry completion | X (ongoing) | | | | | |
| Saliva sample for viral shedding | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [d] | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results may not be reported to sites.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD3152 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

D7000C00001 is a Phase I/III study. The Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442] and AZD3152) in healthy adults. The Phase III Main Cohort will assess the safety and neutralizing activity of AZD3152 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19.

This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan, to AZD3152 through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha. The study will also assess efficacy of two doses of AZD3152 compared with two doses of AZD7442 given at a 6-month interval.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 03 February 2023, has caused over 750 million confirmed cases of COVID-19, including more than 6.8 million deaths, reported to the WHO (WHO 2023). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective,

this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated continued development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 AZD5156, AZD3152, and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD3152 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the past Omicron

variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156 was anticipated to have potent in vitro neutralization activity for all known current and past VOCs.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD3152 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD3152 builds upon the established safety and efficacy of AZD7442. AZD3152 is expected to have a similar safety and PK profile and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD3152 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD3152 are similar to those of the component mAbs of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, BF.7, XBB, and XBB.1 for AZD3152 are superior to those of AZD7442.
- AZD7442 has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD3152 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other

situations where development of a broader protecting mAb such as AZD3152 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 and AZD3152 are provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 and AZD3152 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156/AZD3152 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection

involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. This is not expected with AZD5156 or AZD3152 because, similar to AZD7442, they have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 and AZD3152 studies.

### 2.3.2 Benefit Assessment

AZD5156 and AZD3152 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022). It should be noted that the comparator AZD7442, as well as AZD3152 and AZD5156, may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD3152 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Overall, it is considered that the AZD5156 and AZD3152 nonclinical data available to date, and clinical data from similar mAbs, including AZD7442 (EVUSHELD), provide confidence that the overall benefit-risk is favorable.

Detailed information about the known and expected benefits and potential risks of AZD5156/AZD3152 and AZD7442 is provided in the respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD3152 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the efficacy of AZD3152 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus AZD7442) using a hazard regression model. |
| To compare the nAb responses to the SARS-CoV-2 Omicron variants BA.2 and/or BA.4/5 and the emerging variants of concern circulating during the course of the study in serum following AZD3152 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA |
| **Objectives** | **Estimand Description/Endpoints** |

| **Exploratory** | |
|---|---|
| To assess the PK of AZD5156, AZD3152, and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD3152 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD3152 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits<br>Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD3152 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD3152 compared with AZD7442 for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. The study will be conducted globally.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with AZD7442.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061

[cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the sentinel cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable (for more details on the safety review, see Section 4.1.1). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg (to maintain the blind, each administration of AZD3152 in the Main Cohort will comprise of one injection of AZD3152 and one injection of placebo) or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original

randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD3152 300 mg plus placebo or AZD7442 600 mg) will be administered as 2 sequential IM injections in the thigh, one injection for each component, with the second injection administered in the contralateral side. For participants assigned to AZD3152, AZD3152 should be administered first followed by placebo. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants in the Sentinel Safety and Main Cohorts should refrain from receiving SARS-CoV-2 vaccines until 29 days after receipt of study intervention.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first 56 participants in the study will comprise the Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to

receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants.

The ESDRs for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- Enrollment will be paused once 14 participants have been recruited in the initial cohorts (1a and 1b). Initial ESDRs will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDRs, enrollment of participants will continue to be paused until after Day 15. If the ESDRs conclude that the safety profile is acceptable, then enrollment will be permitted to continue, and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- Enrollment will be paused once more when 42 participants have been recruited into the final 2 cohorts (2a and 2b). Further ESDRs will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile. There is not expected to be any difference in safety profile between AZD3152 administered in combination with AZD1061 (as AZD5156) or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The safety data collected will be entered into eCRFs and reviewed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDRs:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152).

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg plus placebo or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD3152 300 mg plus placebo [a] (1600) | AZD7442 600 mg (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants
[a] Placebo injection administered to maintain the blind.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Section 4.1.1.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021,

Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

A separate dose exploration study (D7000C00004) will be conducted to evaluate the safety and pharmacokinetics of AZD3152.

Participants in the Main Cohort will be randomized to AZD3152 plus placebo (instead of the originally planned AZD5156) or AZD7442. The initial development plan for AZD5156 focused on a combination of two mAbs (cilgavimab [AZD1061] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration.

Main Cohort participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses. The assigned study intervention will be administered as 2 sequential IM injections, one injection for each component, with the second injection administered in the contralateral side to limit the injection volume into the muscle to reduce the risk of local site reactions.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion

criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase III studies. Given the expected safety and PK profile of AZD3152, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD3152 clinical development plan. The adolescent population was approved for EVUSHELD based on PK extrapolation.

### 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort

Despite the current decline in neutralizing activity of AZD7442 in some markets, AstraZeneca consider AZD7442 a more appropriate comparator for the Main Cohort than placebo. In the Main Cohort of the SUPERNOVA study, the participants will receive mAbs whose safety profile is expected to be very similar, and therefore all participants in the Main Cohort will receive at least some protection against SARS-CoV-2.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in the Sentinel Safety Cohort of this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD3152 Dose

The AZD5156 600 mg dose comprises AZD3152 300 mg and AZD1061 300 mg; therefore, AZD3152 300 mg will be used as the dose in the study (see Section 4.3.1). A 300 mg dose of AZD3152 is predicted to maintain nasal lining fluid concentrations of AZD3152 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.3 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modeled concentration needed to prevent disease caused by

BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

### 4.3.4 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals in the Sentinel Safety Cohort at low risk of development of severe COVID-19 in order to provide a blinded comparison and to allow objective assessment of the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the AZD7442 Phase I study (D8850C00001).

In the Main Cohort, placebo will be administered IM directly after the administration of AZD3152 in order to maintain the blind against the 2 IM injections for AZD7442.

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

The results from some laboratory samples may not become available until after the study completion date.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
   – Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned

date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

– Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

– The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

– All female participants of childbearing potential must have a negative urine pregnancy test result at screening.

– Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN at screening.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test at Visit 1 and Visit 5.

4 Weight ≥ 40 kg at Visit 1 and Visit 5.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have solid tumor cancer and be on active treatment except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have hematologic malignancy
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary or secondary immunodeficiency (eg, for primary: DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia; eg, for secondary: hemodialysis)

6 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent

representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as

refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study (except where the participant ceased IMP treatment >90 days and is in the follow-up period of the study and not expected to receive further IMP).

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure or unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD3152 (plus placebo) or AZD7442 (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. To maintain the blind, each administration of AZD3152 in the Main Cohort will comprise of one injection of

AZD3152 and one injection of placebo. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials.

AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD3152 in the Main Cohort, label-claim volume per vial is 2 mL. For AZD7442 in the Main Cohort, label-claim volume per vial is 1.5 mL for each component.

AZD5156 (gluteal or thigh) or AZD7442 (in the thigh) will each be administered as 2 sequential IM injections, one injection for each component mAb, with the second injection administered in the contralateral side. AZD3152 will be administered as single IM injection, followed by a single IM injection of placebo (both in the thigh) on the contralateral side. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For participants assigned to AZD3152, AZD3152 should be administered first followed by placebo. For AZD7442, AZD1061 should be administered first followed by AZD8895.

Placebo will be supplied locally by the site. In the Sentinel Safety Cohort placebo will be administered as 2 IM injections, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). In the Main Cohort, placebo will be administered as a single IM injection following an initial injection of AZD3152. Placebo will be administered in the thigh, on the contralateral side to the AZD3152 injection.

**Table 8 Investigational Medicinal Products**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** [a] | **AZD3152 (plus placebo) for Main Cohort** [a,b] | **AZD7442 (AZD1061 + AZD8895) for Main Cohort** | **Placebo for Sentinel Safety Cohort** |
|---|---|---|---|---|
| **Type** | Drug | Drug plus placebo | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD3152 will be supplied as a single vial. Placebo will be supplied by the study site.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Placebo will be 0.9% sodium chloride for injection | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain either 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| Intervention name | AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort [a] | AZD3152 (plus placebo) for Main Cohort [a,b] | AZD7442 (AZD1061 + AZD8895) for Main Cohort | Placebo for Sentinel Safety Cohort |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 300 mg AZD3152 at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 300 mg single dose of AZD3152 | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration [c]** | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections (thigh) of 2 mL each: AZD3152 plus placebo | 2 IM injections (thigh) of 3 mL each | 2 IM injections (gluteal or thigh): 3 mL and 2 mL |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AZD3152: AstraZeneca<br>Placebo: Study site | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | AZD3152: IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement.<br>Placebo: Dependent on study site | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

[b] Placebo injection is to be administered following the initial AZD3152 injection to maintain the blind (number of injections).

[c] The second injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The Investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature-monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156, AZD3152, AZD7442, and placebo for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (ie, the individual

storage time limits are not additive). AZD5156, AZD3152, AZD7442, and placebo do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD3152 (plus placebo) or AZD7442 (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD3152, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system

- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples (including the AstraZeneca Bioanalytical monitor).
- The unblinded Biometric teams (Statisticians and Programmers) both at AstraZeneca and its delegate and the DSMB.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy. SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5.1.2). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. All other vaccines are permitted; however, they should not be given within 14 days before or after Visit 1 dosing of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 14 days before Visit 1 or during the study until at least after Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. The use of vitamins or occasional use of over-the-counter medications (eg, paracetamol, ibuprofen, antihistamines) would not exclude an individual from enrolling in the study.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | All other vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until 29 days after receipt of study intervention. |
| | COVID-19 antivirals | COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks prior to Visit 1 or during the study until after the Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to each dose of IMP. |

IMP = investigational medicinal product; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD3152 plus placebo or AZD7442), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose.

For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated. In the opinion of the Investigator or Sponsor, if any significant events should occur, this should be assessed and decided by the Investigator as to whether the participant should proceed in the study or be discontinued.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156. AstraZeneca will make the final decision after analysis of the safety data.

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any Grade 3 or higher AEs in 2 or more participants, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that, in the opinion of the Sponsor, may preclude further administration of IMP.
- If one or more participant experiences a grade IV hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If two or more participants, within the first 300 participants, experience a grade III or higher hypersensitivity reaction.
- If two or more participants, within the first 300 participants, experience a grade III or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with study intervention until the relevant safety review has been conducted.

If the study is suspended or the decision is made not to proceed to the Main Cohort, a protocol amendment will be submitted to Health Authorities.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, additional Omicron variants such as BA.2 and/or BA.4/5, and the emerging variants circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week. For participants in the Main Cohort, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must be advised to contact the study site as soon as possible.

For participants in the Sentinel Safety Cohort, if SARS-CoV-2 symptoms are reported, an Illness Visit is not required. The participant should be instructed to seek care via their usual healthcare provider.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Main Cohort will be instructed to attend the study site for Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020.

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to

visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

At IL-D1, the study site will issue an Illness e-Diary and train the participant on how and when to complete the e-Diary and document their daily symptoms. Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in the Illness e-Diary. The status of ongoing symptoms reported in the e-Diary at the end of an illness series will be recorded. The end date for any symptoms still present after 14 days will be documented in the eCRF. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.4).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of SARS-CoV-2 Spike protein mutations identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs, and any observations will be documented in the participant's medical records (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Electrocardiograms

A single 12-lead ECGs will be performed at screening (time points specified in the SoA; see Section 1.3). A 12-lead ECG will be obtained after 5 minutes' supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the

Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as unscheduled assessments.

All ECG readings will be digitally stored as source documents.

### 8.2.4 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort (see Section 1.3.1, Section 1.3.2, and Section 1.3.3).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea (or blood urea nitrogen) | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T/I (Main Cohort; screening only) |
| Glucose (random) | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) (or international normalized ratio) |
| **Other (women of childbearing potential only)** | |
| Urine pregnancy test | Follicle stimulating hormone [a] |

[a] For female participants aged < 50 years who are considered postmenopausal, will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal.

For female participants aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts), and using a dipstick test at Visit 1 (both cohorts) and Visit 5 (Main Cohort only). For Visits 1 and 5, urine pregnancy test must be performed and be negative prior to dosing. This is especially important for any female participants who have not reached menarche at enrollment into the study and whose child-bearing potential is expected to change

during the study.

### 8.2.5 Other Safety Assessments

#### 8.2.5.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.5.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling may be recorded in the medical record at site visits.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following administration of study intervention. Serious adverse events, MAAEs, and AESIs will be collected throughout the study.

Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to

- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156, AZD3152, and AZD7442 in this study are based on those identified for EVUSHELD and are as follows:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoAs (Section 1.3).

Medically attended adverse events are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156/AZD3152 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

## 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

### 8.3.10.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

## 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all

relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days**

for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD3152, AZD5156, and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD3152 and AZD7442 from the Main Cohort, AZD5156 from the Sentinel Safety Cohort, and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156, AZD3152, and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, serum and nasal lining fluid PK samples will be collected only for the first 1200 participants (approximately). Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$;
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD5156, AZD3152, and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. For the Main Cohort, samples will be collected only for the first 1200 participants (approximately). Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points

specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD3152.

For storage, re-use and destruction of biomarker samples see Section 8.5.

#### 8.6.2.1 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing peripheral blood mononuclear cells using methods that may include flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor. Samples will be collected at Illness Visit time points specified in the SoAs (Section 1.3). Additionally, plasma may be isolated from the whole blood samples collected to isolate peripheral blood mononuclear cells, which can be utilized for exploratory immunogenicity and biomarker analyses.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants' data will be presented by the dosing regimen received.

## 9.1 Statistical Hypotheses

The primary objectives are to evaluate the safety of AZD3152 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD3152 or AZD7442 in the Main Cohort. Separately, safety and PK of AZD5156 will be evaluated in the Sentinel Safety Cohort.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD3152 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD3152 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD3152 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD3152 (plus placebo) or AZD7442.

A BSSR may be conducted prior to the primary analysis. The overall symptomatic COVID-19 blinded event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may

result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed. Full details will be in a BSSR plan.

The sample size in the Main Cohort is driven by the total number of events required to demonstrate the efficacy of AZD3152 versus AZD7442 in the prevention of symptomatic COVID-19. Approximately 40 events will provide at least 90% to detect HR of 0.3, or a 70% reduction in hazard. Under the assumption that the event rate will be approximately 3.2% AAR in the AZD7442 arm, HR of 0.30 (70% efficacy), significance level of $\alpha = 0.05$, and 10% attrition. A target sample of approximately 3200 participants has been selected to reach the required number of events. Assumptions are based on data from prior studies with AZD7442 and reported estimates of the AAR among those with immunocompromising conditions (Kelly et al 2022).

A sample size of approximately 1200 participants in the Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD3152 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

The Main Cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD3152 compared with 1600 participants receiving EVUSHELD.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Anti-drug antibody analysis set | All participants in the FAS who have a non-missing baseline and at least one non-missing post-baseline anti-drug antibody result. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |
| Immunobridging analysis set | Participants in the FAS who have a baseline and post intervention Day 29 antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

This study is designed to evaluate the safety and neutralizing activity of AZD3152 compared with AZD7442 for pre-exposure prophylaxis of COVID-19. The primary endpoint is a noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received. Methods for controlling multiplicity across endpoints will be presented separately in the SAP for the immunobridging and efficacy analyses.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses.

### 9.4.2 Efficacy

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops symptomatic COVID-19 at any time up to Visit 9 (12 months). Positive cases require a central RT-PCR test and meet the qualifying symptoms satisfying the modified WHO definition of symptomatic COVID-19 (see Section 8.1.2).

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD3152 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Participants who become unblinded to treatment assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding or receipt of the first dose of COVID-19 preventive product. Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic

COVID-19, and will be included in the analysis. Participants who withdraw early from the study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

Other efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against additional Omicron variants such as BA.2 and/or BA.4/5 and the emerging variants circulating during the course of the study will also be evaluated. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Anti-drug Antibody Variables

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and

efficacy will be assessed. Further details are provided in the SAP.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

## 9.5 Planned Analyses

The Sentinel Safety Cohort will be summarized separately from the Main Cohort to support review of safety and PK data. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data only. The remaining two analyses will include all available PK and safety data.

The primary analyses for the Main Cohort will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants in both cohorts have completed their end-of-study visit. An evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID-19 be observed prior to the final analysis. The study will maintain a double-blind period until the primary analysis. To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan; the study team will remain blinded. Participant-level unblinding information will be kept strictly confidential, and the rationale for

any unblinding will be documented. The SAP will describe the 2 planned analyses in greater detail.

If there is a medical need for AZD3152 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee – Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort, as discussed in Section 4.1.1.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but

are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

(a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

(b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 13, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care.

# Appendix F Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 4.0 [16 January 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended to add efficacy as a secondary endpoint to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the Main Cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy of AZD5156 compared with AZD7442. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

The protocol has also been amended to enhance the safety assessments of the Main Cohort, at the request of a Regulatory Authority.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1; noted that the test must return a negative result before dosing | To align with internal guidance for WOCBP |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total) |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Additional assessments of vital signs have been added on Days 8 and 189 of the Main Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Pregnancy test added at Visit 1, with the timing specified as prior to randomization | To align with internal guidance for WOCBP (pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Sample for serum chemistry, hematology, coagulation (local laboratory) will be collected on Days 1, 8, and 29; noted that this assessment is to be performed for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of troponin at screening for the Main Cohort | To increase cardiac safety monitoring |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added the footnote clarifying that home or mobile visits by study staff may substitute for site visits to the Day 1 Illness Visit as well | To ensure sites can perform the Day 1 Illness Visit at home, if needed |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e-Diary and training has been added, along with Investigator site review of e-Diary entry completion | Clarification and for consistency |
| 3 Objectives and Endpoints | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP administration (was previously to Day 29) | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention |
| 3 Objectives and Endpoints | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3 Objectives and Endpoints | References to dominant variants removed | To make the objectives/endpoints less specific |
| 3 Objectives and Endpoints | nAb responses to variant BA.2 will be evaluated | To include current and emerging variants of concern |
| 3 Objectives and Endpoints | Addition of secondary endpoint related to efficacy | Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case will be evaluated as a secondary endpoint |
| 3 Objectives and Endpoints | For the objective '*To characterize the cellular immune responses to SARS-CoV-2*' the following endpoint has been added: *Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing* | To further characterize the cellular immune response |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated. This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total) |
| 4.1 Overall Design | The collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 4.1 Overall Design | Noted that MAAEs will be collected throughout the study | Consistent with added safety endpoint |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #4 has been deleted | Duplication with the original inclusion #7 |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11 (original exclusion #10), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15 (original exclusion #14), hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #3 (original inclusion #4) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on negative rapid antigen test at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #4 (original inclusion #5) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Text regarding participants with cancer in Inclusion #5 (original inclusion #6) has been updated to clarify that those with solid tumor cancer who are included in the study must be on active treatment, excluding the exceptions noted; hematologic malignancy has now been noted as a separate risk factor | This was a Regulatory Authority request |
| 5.2.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12 (original exclusion #11), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Subsection on stopping rules for Main Cohort removed | Replaced with new section on Study Suspension/Early Termination |
| 7.4 Study Suspension/Early Termination | New section | Added for consistency with wording used in AZD7442 studies |
| 8.2.3 Electrocardiograms | New section | Added to describe procedures for ECG |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted that serum chemistry, hematology, coagulation (local laboratory) assessments will be conducted for at least the first 600 participants in the Main Cohort; deleted text stating that clinical safety laboratory assessments will not routinely be performed for the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted (in Table 11) that troponin assessment will be performed in the Main Cohort at screening | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1.1 Determination of Drug Concentration | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.6.2.1 Assessment of Cell-mediated Immune Responses | New section | For consistency with endpoints section |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.7 Data Safety Monitoring Board – Main Cohort | Added MAAEs to the safety parameters that will be assessed as part of the DSMB review | Consistent with MAAEs having been added as a safety endpoint |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Updated footnote to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 1.3 Schedule of Activities | Updated text describing the duration of treatment and follow-up periods from 12 months to 15 months | To reflect the change to the study design to increase the safety collection time |
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Moved the footnote marker for vital signs assessments from dosing days to the overall row header as abnormal vital signs must be repeated at all scheduled vital signs assessments, and not only on dosing days, after the participant has been at rest for at least 5 minutes | Correction for consistency with vital signs assessments for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The numbers of confirmed cases and deaths due to COVID-19 have been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'currently circulating Omicron variants' has been replaced with 'past Omicron variants' | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Specified that cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies | Clarification that these events will be monitored in other AZD5156 studies in addition to the present study |
| 2.3.2 Benefit Assessment | Noted that similarity of AZD5156 to AZD7442 is in terms of structure and mechanism of action | Clarification |
| 2.3.2 Benefit Assessment | Noted that AZD7442 and AZD5156 may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus | Clarification |
| 3 Objectives and Endpoints | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative RT-PCR at baseline to positive at any time up to 6 and 12 months | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 3 Objectives and Endpoints | Minor change to endpoint describing how exploratory samples may be used to align with change in Section 8.5.2.3 | Clarification |
| 4.1 Overall Design | Added that the safety and neutralizing activity of AZD5156 will be compared with AZD7442 for pre-exposure prophylaxis of | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | COVID-19 and that the study will be conducted globally | |
| 4.1 Overall Design | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.1 Overall Design | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1 Overall Design | Added that immediate AEs will be collected for a 1-hour observation period after study intervention administration | Clarification |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Updated text to provide further information on ESDRs | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.2 Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.2 Scientific Rationale for Study Design | Noted that a dose exploration study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.1 Rationale for Administration Site | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions | To further clarify rationale for the administration site |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the threshold (was $IC_{90}$ now $IC_{80}$) | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.1 Inclusion Criteria (Sentinel) | For inclusion #6, clarified that participant must understand and comply with all study requirements/procedures | Clarification |
| 5.2.1 Inclusion Criteria (Main) | For inclusion #7, clarified that participant must understand and comply with all study requirements/procedures (including those at Illness Visits) | Clarification |
| 5.4 Screen Failures | Criteria for rescreening have been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated in the text and in a footnote to Table 8 | Updated to reflect current information |
| 6.1 Study Intervention(s) Administered | Noted in the text and in a footnote to Table 8 that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive the first component of their assigned intervention will all receive the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Added specific details for placebo | Clarification |
| 6.1 Study Intervention(s) Administered | Noted in Table 8 that L-histidine hydrochloride is monohydrate | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage and administration of IMP | Wording added to provide more comprehensive details of IMP storage and administration |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.1 Randomization | Added text that participants will receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention, and those having access to the randomization list during the study | Clarification |
| 6.3.2 Blinding | Removed text about Investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.5 Concomitant Therapy | Minor update to wording regarding the Concomitant Medication eCRF | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the 'Restricted' section in Table 9 | To ensure the correct patient population is enrolled |
| 8 Study Assessments and Procedures | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 8.1.2 Participant-reported COVID-19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | Extra information added regarding e-Diaries and documentation in the eCRF | Updated for clarity |
| 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments | Added text stating that genotypic sequencing analysis and phenotypic characterization would be of SARS-CoV-2 Spike protein mutations rather than of the virus | Clarification |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment, and noted that any observations will | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | be documented in the participant's medical records | |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 8.2.4 Clinical Safety Laboratory Assessments | Included the option for urea results to be reported as blood urea nitrogen, and for prothrombin time results to be reported as international normalized ratio | Clarification |
| 8.2.5.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.5.2 Injection Site Reactions | Noted that diameters of any redness/swelling may be recorded at site visits | Clarification |
| 8.2.5.2 Injection Site Reactions | Removed references to specific time points for the Sentinel Safety Cohort | Those specific details were not needed because reference is made to the SoAs |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Noted that AESIs will be programmatically identified through AE information that is collected in the eCRF | Clarification |
| 8.3.4 Adverse Events of Special Interest | Minor edits made throughout the section | Updated for clarity |
| 8.3.9 Reporting of Serious Adverse Events | Minor change to wording of statement about reporting of SAEs | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.3.11.1 Timelines | Updated wording for SAEs associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.2.3 Additional Serum Immunogenicity | Minor change to statement regarding how exploratory serum samples may be used | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.3 Populations for Analyses | Updated the definition of the SARS-CoV-2 neutralizing antibody analysis set to remove the text 'with quantifiable SARS-CoV-2 serum titers' | This was a Regulatory Authority request related to the inclusion of participants without quantifiable serum titers but who received investigational product |
| 9.3 Populations for Analyses | Updated the definition of the anti-drug antibody analysis set | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.1 General Considerations | Noted that details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses | Clarification |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.4.2 Efficacy | Deleted reference to 'incidence of post treatment COVID-19' as 'incidence of post treatment symptomatic COVID-19' is already specified | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 9.4.4 Anti-drug Antibody Variables | Text regarding anti-drug antibody variables edited, with a reference added to the SAP | To simplify the text to keep the necessary information and refer to the SAP for further details |
| 9.5 Planned Analyses | Added details of analyses for Sentinel Safety Cohort | Clarification |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | team will remain blinded during primary analysis | |
| 9.5 Planned Analyses | Noted that an evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID 19 be observed prior to the final analysis | Clarification |
| 9.7 Data Safety Monitoring Board – Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore, have not been summarized |

**CSP Version 3.0 [09 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort, at the request of a Regulatory Authority.

**Summary of Changes**:

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory | This has been added to assist with making a decision regarding whether a female participant is |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | assessments at screening for the Sentinel Safety Cohort | postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination, vital signs, and injection site reaction monitoring (local reactogenicity) have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Sample for clinical safety laboratory assessments added at Day 1 (predose) for the Sentinel Safety Cohort | To obtain baseline values |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For the vital signs assessment on Day 1 of the Sentinel Safety Cohort, the indicator '(predose)' has been deleted | This has been deleted for reasons of clarity, because Day 1 vital signs are not only assessed predose, and the existing footnote (a) provides specific details of the timings |

**CSP Version 2.0 [02 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

Note: due to a typing error, the word 'imitating' appears several times instead of 'initiating' in this historical Summary of Changes, and reference is made to the fact that '*no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed*'; this should have read 80 adult Main Cohort participants.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version Number: 6.0

Study Intervention:

*Sentinel Safety Cohort*
AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152), and placebo (0.9% sodium chloride for injection)

*Main Cohort*
AZD3152 monoclonal antibody plus placebo (0.9% sodium chloride for injection) and AZD7442 (EVUSHELD™), the active comparator

*Sub-study*
AZD3152 monoclonal antibody and AZD7442 (EVUSHELD), the active comparator

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Brief Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 6.0 | 24-May-2023 |
| CSP Version 5.0 | 07-Feb-2023 |
| CSP Version 4.0 | 16-Jan-2023 |
| CSP Version 3.0 | 09-Dec-2022 |
| CSP Version 2.0 | 02-Dec-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 6.0 [24 May 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended primarily to add a sub-study as an Addendum to the Parent study, to upgrade efficacy to a primary endpoint, and to provide additional clarification of the study design elements that impact the recruitment of the Main Cohort.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page<br>Synopsis<br>2.1 Study Rationale<br>3 Objectives and Endpoints<br>4.1 Overall Design<br>4.2 Scientific Rationale for Study Design<br>9 Statistical Considerations | Efficacy has been upgraded to a primary endpoint<br><br>nAb responses to the SARS-CoV-2 Alpha variant is no longer a primary endpoint for the Main Cohort | To allow the collection of efficacy data to support a 300 mg dose<br><br>In accordance with regulatory guidance, the immunobridging objective will be explored through the sub-study |
| Synopsis<br>2.1 Study Rationale<br>4.1 Overall Design | Added text to introduce the inclusion of a separate SUPERNOVA sub-study as an Addendum | Based on FDA feedback, a sub-study has been added to be conducted in the US only |
| Synopsis<br>3 Objectives and Endpoints | Added AZD5156, AZD3152, and AZD1061, ADA titers to the incidence of ADA endpoint for the secondary objective of ADA response evaluation for the Sentinel Safety Cohort | For clarification. |
| Synopsis<br>3 Objectives and Endpoints<br>8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments<br>9 Statistical Considerations | Revised the secondary endpoint for the Main Cohort for the comparison of the nAb responses to the SARS-CoV-2 variants. The text has been updated to specify Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and AZD7442 administration | To add additional SARS-CoV-2 variants as the primary nAb endpoint with nAb responses to the SARS-CoV-2 Alpha variant was removed |
| Synopsis<br>3 Objectives and Endpoints<br>8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments<br>9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Added text to reflect that additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152 | Additional text was added to ensure additional SARS-CoV-2 variants will be assessed |
| Synopsis<br>3 Objectives and Endpoints | Added AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers to the incidence of ADA endpoint for the secondary objective of ADA response evaluation for the Main Cohort | For clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>4.1 Overall Design<br>4.1.1 Sentinel Safety Cohort<br>9.2 Sample Size Determination | Added "approximately" to "56 healthy adults" | To allow for any small number of additional participants in the Sentinel Safety Cohort |
| Synopsis<br>9 Statistical Considerations | Section has been updated | Changes added to align with the upgrading of efficacy to a primary endpoint and the removal of the primary endpoint of nAb responses to the SARS-CoV-2 Alpha variant |
| 1.3 Schedule of Activities<br>1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Updated the screening period for the Main Cohort participants to "up to 14 days (Day -14 through Day 1)" | To facilitate the collection of medical history information |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Removed the assessment of eligibility criteria verification from Visit 5, and added a new row to verify selected eligibility criteria for receipt of second dose (Visit 5) with footnote [c] to see Section 5.2.3 | To clarify the eligibility criteria for receipt of second dose of study intervention |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added a new footnote [d] to the full physical examination assessment during the Early Discontinuation Visit to exclude height measurement in adults aged 18 years and older during the assessment | For clarification. |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>5.2.2 Exclusion Criteria (Main Cohort)<br>8.2.4 Clinical Safety Laboratory Assessments | Updated the pregnancy testing to reflect that a serum pregnancy test may be substituted for a urine pregnancy test where a urine pregnancy testing is unavailable | This change has been made to allow for pregnancy testing in female participants who are unable to produce urine |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added a new footnote [h] to the rapid antigen test for SARS-CoV-2 (performed locally) assessment at Visit 5 to note that if a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive | To provide flexibility regarding the second dose administration of IMP in participants who have a positive rapid antigen test at Visit 5 and aligned to Section 8.1.3 on Illness Visits. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3) | |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.1.2 Participant-reported COVID-19 Symptoms | Added a new row for assessments of "Monthly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms", adjusted footnote [l] (previous footnote [i]) for clarification | Telephone contact will take place weekly prior to Day 361, and monthly from Day 361 to reduce the site and participant burden |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>4.1 Overall Design<br>8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Added footnote [m] and updated text in Sections 4.1 and 8.3.1 to clarify that AEs occurring after 90 days following each study intervention administration and assessed by the Investigator as having a causal relationship to IMP and/or COVID-19-related but does not prompt and Illness Visit (eg, asymptomatic COVID-19) will be collected on the AE CRF page | This change has been made in case events occur outside of the AE windows (after 90 days following each study intervention) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.5.1.1 Determination of Drug Concentration<br>8.5.2.1 Anti-drug Antibody Assessments | Removed footnote [o] (previous footnote [k]) from assessments of PK serum sample and ADA and antidrug nAbs assessment serum sample and accordingly updated the text in Sections 8.5.1.1 and 8.5.2.1 to clarify that nasal lining fluid PK samples will only be collected for the first 600 participants (previously 1200 participants) | To extend the analysis of PK, ADA, and antidrug nAbs to the full enrolled population<br>Reduced the number of nasal lining fluid samples to 600 as the previous number of 1200 was aligned to the immunobridging endpoint, which has now been removed from this protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added "and 1 hour" to footnote [p] | This change has been made to allow evaluation of safety and tolerability 1 hour after both injections are given and also aligned to Section 8.2.5.2 on Immediate Adverse Events which are assessed 1 hour after both injections |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added a column for the Unscheduled Visit to verify qualifying symptoms with footnote [d] to clarify that if the participant meets the clinical criteria adapted from WHO COVID-19 case definition, then an illness visit (IL-D1) will be initiated | Added a column to clarify the requirements for the Unscheduled Visit and for which an Illness Visit series should be initiated |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Updated the window for Visit IL-D14 to + 2 days | The participant e-Diary will need to be completed up to and including IL-D14 |
| | Updated footnote [e] to reflect that central RT-PCR laboratory test results may not be reported to sites during the Illness Visit period | For clarification |
| | Telephone contact for safety monitoring has been added to the visits IL-D5 and IL-D11 and footnote [f] has been added to note that for the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen | This change has been added to ensure telephone contact is made with the participant on each home Illness Visit |
| | Added “WHO Clinical Progression Scale” assessments to the Illness Visits with footnote [f] for clarification | To clarify that the WHO Clinical Progression Scale score is required for each site Illness Visit |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Changed “Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic” to “Coronavirus SARS-CoV-2 is the causative agent of COVID-19” | Updated to the current WHO status for COVID-19 |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Changed “against the more recent Omicron variants BA.2, BA.3, and BA.4/5” to “against some of the | To add clarity since additional variants have emerged |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | more recent Omicron variants such as BA.2, BA.3, and BA.4/5" | |
| 3 Objectives and Endpoints | Added an exploratory objective to characterize the predicted serum nAb responses to SARS-CoV-2 variants following IMP administration. The endpoint will be descriptive statistics for predicted GMTs will include the number of participants, geometric mean, gSD, 95% CI, summarized by treatment arm and visit for select SARS CoV-2 variants using PK and in-vitro $IC_{50}$ values | To align with the removal of the primary immunobridging endpoint, this exploratory objective has been added to characterise nAb titers associated with each treatment arm |
| 4.1 Overall Design<br>6.5 Concomitant Therapy | Updated text to reflect that SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments, and subsequently should not be given from 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments | The timing of the restriction was re-aligned from Day 29 to the assessments that occur at Visit 3 which may occur up to 3 days post Day 29, as per the 3-day visit window. Restrictions of SARS-CoV-2 vaccines added to the second dose, were included to prevent confusion around possible reactogenicity of the vaccine at the time of the second dose being administered |
| 4.1 Overall Design<br>8.1.2 Participant-reported COVID-19 Symptoms | Updated text to reflect that the clinical criteria for SARS-CoV-2 infection in the protocol is adapted from the WHO COVID-19 case definition and a reference to the most recent WHO COVID-19 case definition (July 2022) has been added | Clinical criteria for SARS CoV-2 infection in this protocol have been adapted from the WHO COVID-19 case definition |
| 5.2.1 Inclusion Criteria (Main Cohort) | Updated Inclusion criterion #3 to reflect that participants should have a negative rapid antigen test prior to dosing at Visit 1 and removed "Visit 5" | This change has been made to note that a negative rapid antigen test must be obtained prior to the first dose of study intervention to confirm eligibility for entry into the study. Visit 5 was removed from the entry criteria given that the participant is already entered into the study, and instead eligibility for the second dose of study intervention will be verified at Visit 5 |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Updated Inclusion criterion #4 to reflect that participants weights should be ≥ 40 kg at screening and removed "Visit 5" | To ensure that the participant has a safe weight for receiving study intervention to confirm eligibility for entry into the study. Visit 5 was removed from the entry criteria given that the participant is already entered into the study, and instead eligibility for the second dose of study intervention will be verified at Visit 5 |
| | For Inclusion criterion #5, changed "active treatment" to "active immunosuppressive treatment" (first bullet), and removed the examples | To clarify the active treatment must be immunosuppressive. The examples were excluded as they would not meet the new definition |
| | Updated the inclusion criteria of participants who previously had a transplant (third bullet) | To clarify the inclusion of participants who previously had a transplant |
| | Changed "other immunosuppressive or immunomodulatory biologic agents" to "other immunosuppressive biologic agents" (fourth bullet) | To ensure that the entry criteria include those participants who are on medication that leave them immunosuppressed |
| | Removed "Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia" (seventh bullet) | Text removed to be consistent with Exclusion criterion #8 regarding the use of IVIG and SCIG |
| | For Inclusion criterion #6, changed "change in therapy" to "change in maintenance therapy" and added "or any recent cardiovascular event (eg, acute myocardial infarction, thromboembolic event)" | Added language around therapy for clarification, and additional language including cardiovascular events to ensure participant is medically stable prior to study entry |
| 5.2.2 Exclusion Criteria (Main Cohort) | Updated Exclusion criterion #1 to include a negative serum pregnancy and that a negative urine or serum pregnancy test must be obtained prior to Visit 1 | This change was made because a urine pregnancy test is not possible in all female participants and to note that a negative pregnancy test should be obtained prior to both the first and second dose of study intervention |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Added Exclusion criterion #8, to state that participants being treated with intravenous or subcutaneous immunoglobulins (IVIG or SCIG) within 6 months prior to Visit 1 or are expected to receive IVIG or SCIG within 6 months after dosing should be excluded from the study | IVIG/SCIG treatment may confound the neutralizing antibody results |
| 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5 | New section | This section has been added to clarify the eligibility criteria prior to receipt of the second dose of study intervention at Visit 5 |
| 5.4 Screen Failures | Updated the text to remove the 2-week window in which the single rescreening could occur and added text to specify that the rescreening can occur at any time during the enrollment period | Removed the 2-week window to reflect the immunocompromised population |
| 6.1 Study Intervention(s) Administered | Updated Table 8 to indicate how many vials are required to constitute AZD1061, AZ8895, and AZ3152 | For clarification |
| 6.5 Concomitant Therapy | Updated Table 9 to reflect that participants must not have COVID-19 antivirals for prophylaxis 2 weeks prior to Visit 1, and during the study until after the Day 29 assessments following the first dose, and after the Day 210 assessments following the second dose of study intervention | This change was made to note that the restrictions for COVID-19 antivirals applies to both the first and second dose of study intervention, so as to avoid confounding the results of the immune sampling. The timing of the restriction was re-aligned from Day 29 and Day 210 to the assessments that occur at Visit 3 and Visit 7 which may occur up to 3 days post Day 29 and Day 210 respectively, as per the 3-day visit window |
| | Updated Table 9 to include intravenous or subcutaneous immunoglobulins (IVIG or SCIG) in “restricted” | IVIG/SCIG treatment may confound the study results and therefore, has been excluded from the study |
| | Updated Table 9 to reflect EVUSHELD should not be given within 6 months prior to each dose of IMP and until 6 months after the last dose of IMP | EVUSHELD treatment may confound the study results and therefore the criteria around the timing have been clarified |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.1 Discontinuation of Study Intervention | Updated the text to reflect that if the participant experiences an immediate hypersensitivity reaction after either IM injection, the participant will be excluded from receiving a second dose of study intervention at Visit 5 and that the participant will continue in the study and complete all scheduled assessments and sampling to end of the study | Clarification around receiving the second dose following hypersensitivity reactions |
| | Updated the text to reflect that participants who miss or are not eligible to receive the second dose of study intervention will continue in the study and complete all scheduled assessments and sampling to end of the study | For clarification |
| 7.2.2 Stopping Rules for Main Cohort | New section | Section 7.2.2 has been added to specify stopping rules for the Main Cohort |
| 8.1.2 Participant-reported COVID-19 Symptoms | Updated text to clarify the participants for which an Unscheduled Visit should be conducted and for which an Illness Visit series should be initiated | Clarified the participants for which an Unscheduled Visit should be conducted and for which an Illness Visit series should be initiated |
| | Updated the clinical criteria for SARS-CoV-2 infection based on those adapted from the WHO COVID-19 case definition | Clinical criteria for SARS-CoV-2 infection in this protocol have been adapted from the WHO COVID-19 case definition to account for a positive COVID-19 test performed off-site and any potential new symptoms that could develop given the rapidly changing landscape of COVID-19 variants |
| | Clarified that fever is subjective for the clinical criteria adapted from WHO COVID-19 case definition | Updated to clarify that a subjective assessment of fever will be utilized |
| | Added text to define fever for severe COVID -19 at ≥ 38°C. | For clarification. |
| 8.1.3 Illness Visits | Text added to reflect that the study site will set up an illness e-Diary on the participant's own device (if available) as the primary approach | For clarification. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Text added to reflect that for the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen | Clarification provided to ensure study sites follow-up with the participants for symptoms and safety information |
| | Text added to state that Visit 5 (administration of the second dose of IMP) is only allowed to overlap with IL-D14. If Visit 5 is scheduled to occur at any of the other Illness Visit days, it should be delayed to IL-D14. | To prevent IMP dosing during an Illness Visit assessment pathway. |
| 8.2.3 Electrocardiograms | Added text to clarify that a single 12-lead ECG will be performed at screening for the Sentinel Safety Cohort and Main Cohort | For clarification |
| | Changed “normal or abnormal” to “normal, borderline, or abnormal” | For clarification |
| 8.2.5.2 Injection Site Reactions | Added text to state that injection site monitoring will also be performed at 1 hour after both injections for the study intervention dose are given, and that injection site reactions will be monitored on on Visit 2 (Day 3), Visit 3 (Day 5) and Visit 4 (Day 8) for the Sentinel Study and Visit 2a (Day 8) and Visit 6 (Day 189) for the Main Study | This change has been made to align with Section 8.2.5.2 on Immediate Adverse Events which are assessed 1 hour after both injections |
| 8.3.2 Follow-up of AEs and SAEs | Removed “maximum severity grade” from adverse event variables | Maximum severity grade will be derived and therefore is not required to be collected from the CRF |
| 8.3.5 Medically Attended Adverse Events | Added text to clarify that Illness Visits themselves will not be considered as MAAEs | Clinic visits for scheduled procedures are not considered MAAEs |
| 8.3.10.1 Maternal Exposure | Added text to state that the IMP should not be given to pregnant women | For clarification of safety requirements |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.5.2.1 Anti-drug Antibody Assessments | Updated ADA to AZD1061, AZD3152, and AZD8895 will be determined (removed AZD5156 and AZD7442) | To clarify individual monoclonal antibodies to be evaluated. |
| Appendix F List of Immunosuppressive Medications | Added a new Appendix | To clarify which medications taken by participants will qualify them as immunocompromised |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms<br>4.1 Overall Design<br>8.1.3 Illness Visits | Updated text to clarify that duplicate sampling is not required where Main and Illness Visits overlap and added a reference to the Laboratory Manual | For clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | Changed “some markets” to “some regions”<br>Changed “at least some protection against SARS-CoV-2” to “at least some potential protection against SARS-CoV-2” | For clarification |
| 6.5 Concomitant Therapy | Changed “All other vaccines” to “All routine vaccines” | For consistency with Table 9 |
| 8.1.3 Illness Visits | Changed “site visits” to “site illness visits”<br>Added “up to 10 times” for Illness Visit initiations | For clarification<br>For clarification |
| 8.2.2 Vital Signs | Changed “after both injections” to “after the second injection” | This change has been made to clarify that vital signs will be monitored at 10 to 15 minutes after the second injection of the dose of study intervention is given |
| 8.2.3 Electrocardiograms | Added text to clarify that a single 12-lead ECG will be performed at screening for the Sentinel Safety Cohort and Main Cohort | For clarification |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |

| Abbreviation or special term | Explanation |
|---|---|
| GMFR | Geometric Mean Fold Rise |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| hCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{50}$ | Concentration giving half-maximal inhibition |
| $IC_{80}$ | Concentration required for 80% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IVIG | Intravenous immunoglobulins |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |

| Abbreviation or special term | Explanation |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SCIG | Subcutaneous immunoglobulins |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD3152 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

D7000C00001 is a Phase I/III study that comprises a Parent study and a sub-study. In the Parent study, the Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442] and AZD3152) in healthy adults and the Phase III Main Cohort will assess the safety, efficacy, PK, and neutralizing activity of two doses of AZD3152 compared with two doses of AZD7442 given at a 6-month interval in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and AZD7442.

The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA to AZD5156, AZD3152, and AZD1061, ADA titers |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the efficacy of AZD3152 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 3706 participants (approximately 3256 in the Parent study and 450 in the sub-study) to evaluate the safety, efficacy, PK, and neutralizing activity of AZD3152 compared with AZD7442 for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. D7000C00001 is a Phase I/III study that comprises a Parent study and a sub-study; all details for the sub-study are described in an Addendum.

The Parent study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with AZD7442.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg (to maintain the blind, each administration of AZD3152 in the Main Cohort will comprise of one injection of AZD3152 and one injection of placebo) or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD3152 300 mg plus placebo or AZD7442 600 mg) will be administered as 2 sequential IM injections in the thigh, one injection for each component, with the second injection administered in the contralateral side. For participants assigned to AZD3152, AZD3152 should be administered first followed by placebo. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used

at each trial site; the participant and Investigator will be blinded to study intervention). Participants from the Main Cohort will receive a second dose of their assigned study intervention, approximately 6 months after their first dose.

**Number of Participants:**

Approximately 3256 participants will be randomized in the Parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD3152 (plus placebo) or AZD7442.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: 1 dose of AZD3152 300 mg IM and 1 dose of placebo (to maintain the blind) (on 2 occasions with a 6-month interval) or AZD7442 600 mg IM (on 2 occasions with a 6-month interval).

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Sentinel Safety Cohort as follows: after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b), and subsequently after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 subcohorts, prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

**Statistical Methods**

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK concentrations at Day 29. The remaining two analyses will include all available data when conducted. The primary analysis for the Main Cohort will be conducted by a limited unblinded team after approximately 40 or more participants have met conditions for the primary efficacy endpoint.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD3152 and AZD7442 and to compare the efficacy of AZD3152 versus AZD7442 in the Main Cohort for the prevention of symptomatic COVID-19. Separately, safety and PK of AZD5156 will be evaluated in the Sentinel Safety Cohort.

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops their first symptoms for COVID-19 at any time up to Visit 9 (Day 361). Positive cases require a central RT-PCR test and meet the qualifying symptoms as indicated by the Investigator satisfying the modified WHO definition of symptomatic COVID-19. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to compare prophylactic efficacy (ie, 1-HR) of AZD3152 versus AZD7442.

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

Efficacy Endpoints

Other COVID-19 efficacy endpoints are derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis of secondary efficacy endpoints.

SARS-CoV-2 nAb Response

The secondary endpoints of nAb responses against SARS-CoV-2 variants, including Alpha, Omicron BA.2, Omicron BA.4/5 and Omicron XBB.1.5 will be evaluated using the geometric mean titer (GMT) ratio between treatment arms. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152.

Characterization of PK

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of these 2 component mAbs of AZD5156. The following single dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

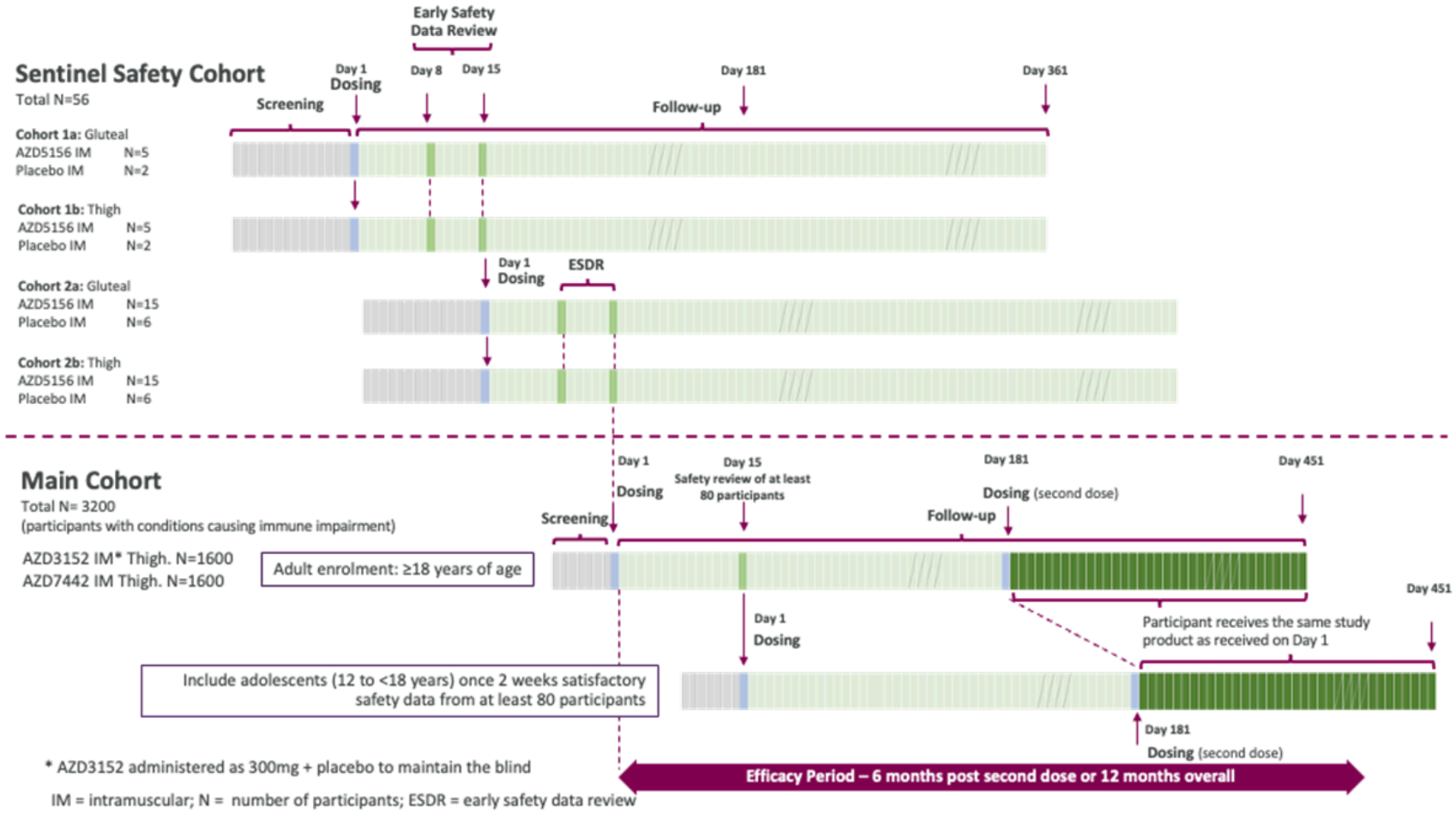
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.
Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort (data up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b), and then prior to enrollment of the Main Cohort.
Note: Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 14 days (Day -14 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| 12-Lead electrocardiogram (single, to be performed locally) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [f] | X | X | X | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | | | | | | | |
| Verify selected eligibility criteria for receipt of second dose (Visit 5) [c] | | | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | Weight only (predose) | | | | | | X [d] |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [e] | X | X | X | | | | X | X | | | | | |
| 12-lead electrocardiogram (single, to be performed locally) | X | | | | | | | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Urine or serum β-hCG pregnancy test (WOCBP only, local laboratory) [f] | X | X (predose) | | | | | X (predose) | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [g] | | X (predose) | | | | | X [h] (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [i] (predose) | | | | | X [i] (predose) | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) [j] | | X (predose) | X | | X | | | | | | | | |
| Troponin T or I | X | | | | | | | | | | | | |
| Follicle stimulating hormone [k] | X | | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [l] | | X ← → | | | | | | | | | | | |
| Monthly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [l] | | | | | | | | | | | ← → | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Assessment of AEs [m] | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |
| PK serum sample [n] | | X (predose) | | | X | X | X (predose) | X | X | | X | | |
| PK nasal lining fluid sample [o] | | X (predose) | | | X | X | | | | | | | |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | | X | | |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [p] | X | | | | X [p] | X | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Immediate AEs [q] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] See Section 5.2.3 for the eligibility criteria for the receipt of the second dose of study intervention at Visit 5.
[d] Excludes height measurement in adults aged 18 years and older.
[e] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[f] Sample urine or serum β-hCG pregnancy test must return a negative result before dosing. Pregnancy testing prior to each dose must be on the same day as dosing and is especially important for female participants who had not reached menarche on enrollment into the study.
[g] Sites will be provided with rapid antigen tests.
[h] If a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3).
[i] To be collected at baseline. The results are not needed prior to dosing.
[j] To be performed for at least the first 600 participants in the Main Cohort.
[k] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[l] Weekly (prior to Day 361) and then monthly (from Day 361) contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The weekly and monthly telephone calls should be performed in addition to any scheduled site visits.
[m] Adverse events that occur outside of the 90-day window between each study intervention administration that are either related to IMP, or are COVID-19-related but do not prompt an Illness Visit (eg, asymptomatic COVID-19), will be reported on the AE CRF page.
[n] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[o] Samples collected only for the first 600 participants (approximately) in the Main Cohort.
[p] Perform immediately, 30 minutes (+ 10 minutes) and 1 hour after both injections are complete, and prior to participant release.
[q] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; β-hCG = beta human chorionic gonadotropin; CRF = case report form; EDV = Early Discontinuation Visit; IMP = investigational medicinal product; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Unscheduled Visit** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|---|
| **Day [c]** | | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **+ 2** |
| Verify qualifying clinical symptoms [d] | X | | | | | | |
| Medical history | | X | | | X | | X |
| Targeted physical examination | | X | | | X | | X |
| Vital signs (including pulse oximetry) | | X | | | X | | X |
| Set up of e-Diary and training | | X | | | | | |
| Assessment of AEs, SAEs, MAAEs, and AESIs | | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily for 14 days by participant in Illness e-Diary) | | X ← → | | | | | |
| Investigator site review of e-Diary entry completion | | X (ongoing) | | | | | |
| Saliva sample for viral shedding | | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | | X | | | X | | X |
| PBMCs for T-cell responses | | X | | | X | | X |
| PK serum sample | | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Unscheduled Visit** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|---|
| **Day [c]** | | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **+ 2** |
| SARS-CoV-2 neutralizing antibody serum sample | | X | | | X | | X |
| Exploratory analysis serum sample | | X | | | X | | X |
| Telephone contact for safety monitoring [f] | | | X | X | | X | |
| WHO Clinical Progression Scale [f] | | X | X | X | X | X | X |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] If the participant meets the clinical criteria adapted from the WHO COVID-19 case definition (see Section 8.1.2), then an illness visit (IL-D1) will be initiated.

[e] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results may not be reported to sites during the Illness Visit period.

[f] For the duration of the Illness Visit period, sites should follow up with the participant either at the site visit or by telephone for home visits to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD3152 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

D7000C00001 is a Phase I/III study that comprises a Parent study and a sub-study. In the Parent study, the Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442] and AZD3152) in healthy adults and the Phase III Main Cohort will assess the safety, efficacy, PK, and neutralizing activity of two doses of AZD3152 compared with two doses of AZD7442 given at a 6-month interval in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and AZD7442.

The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of COVID-19 that, as of 17 May 2023, has caused over 760 million confirmed cases of COVID-19, including more than 6.9 million deaths, reported to the WHO (WHO 2023). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated continued development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 AZD5156, AZD3152, and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against some of the more recent Omicron variants such as BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD3152 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the past Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156

was anticipated to have potent in vitro neutralization activity for all known current and past VOCs.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD3152 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD3152 builds upon the established safety and efficacy of AZD7442. AZD3152 is expected to have a similar safety and PK profile and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD3152 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD3152 are similar to those of the component mAbs of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, BF.7, XBB, and XBB.1 for AZD3152 are superior to those of AZD7442.
- AZD7442 has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD3152 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD3152 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the

protection acquired from currently available vaccines.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 and AZD3152 are provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 and AZD3152 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156/AZD3152 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. This is not expected with AZD5156 or AZD3152 because, similar to AZD7442, they have been designed with a modification to prevent binding to cellular Fc

receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 and AZD3152 studies.

### 2.3.2 Benefit Assessment

AZD5156 and AZD3152 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline as shown in the Phase III PROVENT trial (Levin et al 2022). It should be noted that the comparator AZD7442, as well as AZD3152 and AZD5156, may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD3152 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Overall, it is considered that the AZD5156 and AZD3152 nonclinical data available to date, and clinical data from similar mAbs, including AZD7442 (EVUSHELD), provide confidence that the overall benefit-risk is favorable.

Detailed information about the known and expected benefits and potential risks of AZD5156/AZD3152 and AZD7442 is provided in the respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA to AZD5156, AZD3152, and AZD1061, ADA titers |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the efficacy of AZD3152 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus AZD7442) using a hazard regression model. |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers |
| **Exploratory** | |
| To assess the PK of AZD5156, AZD3152, and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD3152 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD3152 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits<br>Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD3152 | Other exploratory assays for humoral, mucosal, and cellular immune responses, including additional SARS-CoV-2 nAB, may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| To characterize the predicted serum nAb responses to SARS-CoV-2 variants following IMP administration | Descriptive statistics for predicted GMTs will include the number of participants, geometric mean, gSD, 95% CI, summarized by treatment arm and visit for select SARS-CoV-2 variants using PK and in-vitro $IC_{50}$ values [a] |

[a] $IC_{50}$ values from prior in-vitro analysis of AZD3152 and AZD7442 in research grade pseudovirus neutralization assays will be used.

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; $IC_{50}$ = concentration giving half-maximal inhibition; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 3706 participants (approximately 3256 in the Parent study and 450 in the sub-study) to evaluate the safety, efficacy, PK, and neutralizing activity of AZD3152 compared with AZD7442 for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. The study will be conducted globally. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum. The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and AZD7442.

The Parent study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with AZD7442.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with

AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the sentinel cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable (for more details on the safety review, see Section 4.1.1). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg (to maintain the blind, each administration of AZD3152 in the Main Cohort will comprise of one injection of AZD3152 and one injection of placebo) or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately

15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD3152 300 mg plus placebo or AZD7442 600 mg) will be administered as 2 sequential IM injections in the thigh, one injection for each component, with the second injection administered in the contralateral side. For participants assigned to AZD3152, AZD3152 should be administered first followed by placebo. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. For the Main Cohort, AEs that occur outside of these windows between each administration that are either related to IMP, or are COVID-19 related but do not prompt an Illness Visit (eg, asymptomatic COVID-19), will be reported on the AE CRF page. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (adapted from the WHO COVID-19 case definition WHO 2022) and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants in the Sentinel Safety and Main Cohorts should refrain from receiving SARS-CoV-2 vaccines until after the Day 29 assessments have been completed. For participants in the Main Cohort, SARS-CoV-2 vaccines should not be given 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first approximately 56 participants in the study will comprise the Sentinel Safety Cohort.

Healthy adults 18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants.

The ESDRs for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- Enrollment will be paused once 14 participants have been recruited in the initial cohorts (1a and 1b). Initial ESDRs will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDRs, enrollment of participants will continue to be paused until after Day 15. If the ESDRs conclude that the safety profile is acceptable, then enrollment will be permitted to continue, and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- Enrollment will be paused once more when 42 participants have been recruited into the final 2 cohorts (2a and 2b). Further ESDRs will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile. There is not expected to be any difference in safety profile between AZD3152 administered in combination with AZD1061 (as AZD5156) or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The safety data collected will be entered into eCRFs and reviewed. These reviews will be

based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDRs:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152).

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg plus placebo or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD3152 300 mg plus placebo [a] (1600) | AZD7442 600 mg (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants
[a] Placebo injection administered to maintain the blind.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Section 4.1.1.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure

prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and efficacy.

A separate dose exploration study (D7000C00004) will be conducted to evaluate the safety and pharmacokinetics of AZD3152.

Participants in the Main Cohort will be randomized to AZD3152 plus placebo (instead of the originally planned AZD5156) or AZD7442. The initial development plan for AZD5156 focused on a combination of two mAbs (cilgavimab [AZD1061] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration.

Main Cohort participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses. The assigned study intervention will be administered as 2 sequential IM injections, one injection for each component, with the second injection administered in the contralateral side to limit the injection volume into the muscle to reduce the risk of local site reactions.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using

AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase III studies. Given the expected safety and PK profile of AZD3152, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD3152 clinical development plan. The adolescent population was approved for EVUSHELD based on PK extrapolation.

### 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort

Despite the current decline in neutralizing activity of AZD7442 in some regions, AstraZeneca consider AZD7442 a more appropriate comparator for the Main Cohort than placebo. In the Main Cohort of the SUPERNOVA study, the participants will receive mAbs whose safety profile is expected to be very similar, and therefore all participants in the Main Cohort will receive at least some potential protection against SARS-CoV-2.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in the Sentinel Safety Cohort of this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD3152 Dose

The AZD5156 600 mg dose comprises AZD3152 300 mg and AZD1061 300 mg; therefore, AZD3152 300 mg will be used as the dose in the study (see Section 4.3.1). A 300 mg dose of AZD3152 is predicted to maintain nasal lining fluid concentrations of AZD3152 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.3 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modeled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

### 4.3.4 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals in the Sentinel Safety Cohort at low risk of development of severe COVID-19 in order to provide a blinded comparison and to allow objective assessment of the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the AZD7442 Phase I study (D8850C00001).

In the Main Cohort, placebo will be administered IM directly after the administration of AZD3152 in order to maintain the blind against the 2 IM injections for AZD7442.

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of

the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

The results from some laboratory samples may not become available until after the study completion date.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN at screening.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test prior to dosing at Visit 1.

4 Weight ≥ 40 kg at screening.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have solid tumor cancer and be on active immunosuppressive treatment
- Have hematologic malignancy
- Transplant participants must satisfy at least one of the following:
  - Have had a solid organ transplant within 2 years and / or
  - Had a hematopoietic stem cell transplant within 2 years and / or
  - Who have chronic graft-versus-host disease
  - Participants who previously had a solid organ transplant or hematopoietic stem cell transplant more than 2 years prior to Visit 1 may also be eligible based on the inclusion criterion for immunosuppressive treatment
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive biologic agents (eg, for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary or secondary immunodeficiency (eg, for primary: DiGeorge syndrome; eg, for secondary: hemodialysis)

See Appendix F for the list of qualifying immunosuppressive medications.

6 Medically stable defined as disease not requiring significant change in maintenance therapy or hospitalization for worsening disease or any recent cardiovascular event (eg, acute myocardial infarction, thromboembolic event) during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine or serum (β-hCG) pregnancy test result at screening and prior to Visit 1 before the administration of study intervention.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of IV or SC immunoglobulin within 6 months prior to Visit 1 or expected to receive IV and SC immunoglobulin 6 months after dosing.

9 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

10 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

11 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

12 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

13 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

14 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study (except

where the participant ceased IMP treatment >90 days and is in the follow-up period of the study and not expected to receive further IMP).

15 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

16 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

17 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

18 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

### 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5

Prior to receipt of the second dose of study intervention at Visit 5, participants should:

1 Have a negative rapid antigen test* for SARS-CoV-2.

2 Have a body weight ≥ 40 kg.

3 Have a negative serum or urine pregnancy test for female participants.

4 Not have received IV or SC immunoglobulin within 6 months prior to the second dose at Visit 5 or are expected to receive IV and SC immunoglobulin 6 months after dosing.

5 Not have received a COVID-19 vaccine within 14 days prior to the second dose at Visit 5.

6 Not have received COVID-19 antiviral for prophylaxis within 2 weeks prior to the second dose at Visit 5.

*If a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3).

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure

information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure or unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study, which can occur at any time during the enrollment period. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD3152 (plus placebo) or AZD7442 (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. To maintain the blind, each administration of AZD3152 in the Main Cohort will comprise of one injection of AZD3152 and one injection of placebo. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials.

AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD3152 in the Main Cohort, label-claim volume per vial is 2 mL. For AZD7442 in the Main Cohort, label-claim volume per vial is 1.5 mL for each component.

AZD5156 (gluteal or thigh) or AZD7442 (in the thigh) will each be administered as 2 sequential IM injections, one injection for each component mAb, with the second injection administered in the contralateral side. AZD3152 will be administered as single IM injection, followed by a single IM injection of placebo (both in the thigh) on the contralateral side. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For participants assigned to AZD3152, AZD3152 should be administered first followed by placebo. For AZD7442, AZD1061 should be administered first followed by AZD8895.

Placebo will be supplied locally by the site. In the Sentinel Safety Cohort placebo will be administered as 2 IM injections, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). In the Main Cohort, placebo will be administered as a single IM injection following an initial injection of AZD3152. Placebo will be administered in the thigh, on the contralateral side to the AZD3152 injection.

**Table 8 Investigational Medicinal Products**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** [a] | **AZD3152 (plus placebo) for Main Cohort** [a,b] | **AZD7442 (AZD1061 + AZD8895) for Main Cohort** | **Placebo for Sentinel Safety Cohort** |
|---|---|---|---|---|
| **Type** | Drug | Drug plus placebo | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD3152 will be supplied as a single vial. Placebo will be supplied by the study site.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Placebo will be 0.9% sodium chloride for injection | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain either 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| Intervention name | AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort [a] | AZD3152 (plus placebo) for Main Cohort [a,b] | AZD7442 (AZD1061 + AZD8895) for Main Cohort | Placebo for Sentinel Safety Cohort |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 300 mg AZD3152 at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 300 mg single dose of AZD3152 | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Vials required for constitution** | AZD1061; 2 vials<br>AZD3152; 1 vial | AZD3152; 1 vial | AZD1061; 2 vials<br>AZD8895; 2 vials | NA |
| **Route of administration [c]** | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections (thigh) of 2 mL each: AZD3152 plus placebo | 2 IM injections (thigh) of 3 mL each | 2 IM injections (gluteal or thigh): 3 mL and 2 mL |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AZD3152: AstraZeneca<br>Placebo: Study site | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | AZD3152: IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement.<br>Placebo: Dependent on study site | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

[b] Placebo injection is to be administered following the initial AZD3152 injection to maintain the blind (number of injections).

[c] The second injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The Investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156, AZD3152, AZD7442, and placebo for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (ie, the individual

storage time limits are not additive). AZD5156, AZD3152, AZD7442, and placebo do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD3152 (plus placebo) or AZD7442 (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD3152, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system

- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples (including the AstraZeneca Bioanalytical monitor).
- The unblinded Biometric teams (Statisticians and Programmers) both at AstraZeneca and its delegate and the DSMB.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy. SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5.1.2). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. All routine vaccines are permitted; however, they should not be given within 14 days before or after Visit 1 dosing of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 14 days before Visit 1 or during the study until at least after Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. The use of vitamins or occasional use of over-the-counter medications (eg, paracetamol, ibuprofen, antihistamines) would not exclude an individual from enrolling in the study.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | All routine vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments, and subsequently should not be given from 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks prior to Visit 1 or during the study until after the Day 29 assessments following the first dose, and after the Day 210 assessments (Visit 5) following the second dose of study intervention. If the participant develops COVID-19, standard of care treatment is allowed. |
| | Immunoglobulins (IVIG or SCIG) | Receipt of IV or SC immunoglobulin within 6 months prior to Visit 1 or expected to receive IV and SC immunoglobulin 6 months after each dose. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to the first dose of IMP and until 6 months after the last dose of IMP. |

IMP = investigational medicinal product; IVIG = intravenous immunoglobulins; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCIG = subcutaneous immunoglobulins.

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD3152 plus placebo or AZD7442), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose.

For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. Also, if the participant experiences an immediate hypersensitivity reaction after either IM injection, the participant will be excluded from receiving a second dose of study intervention at Visit 5. If either of these events occur, the participant should remain in the study to be evaluated and complete all the remaining assessments as indicated in the SoA (Section 1.3). Also, if the participant is not eligible for the second dose (Visit 5), the participant should remain in the study to be evaluated and complete all the remaining assessments as indicated in the SoA. In the opinion of the Investigator or Sponsor, if any significant events should occur, this should be assessed and decided by the Investigator as to whether the participant should proceed in the study or be discontinued.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed

(Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156. AstraZeneca will make the final decision after analysis of the safety data.

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any Grade 3 or higher AEs in 2 or more participants, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Main Cohort

The study will be put on temporary hold (defined as a pause in enrollment and/or dosing of participants into the Main Cohort) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of

AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In the event of a temporary hold for safety reasons, AstraZeneca will carefully review the totality of data and the risk to all participants will be evaluated thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing. If AstraZeneca determines that the study may be resumed, this may occur without a protocol amendment.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a

component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that, in the opinion of the Sponsor, may preclude further administration of IMP.
- If one or more participant experiences a grade IV hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If two or more participants, within the first 300 participants, experience a grade III or higher hypersensitivity reaction.
- If two or more participants, within the first 300 participants, experience a grade III or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with study intervention until the relevant safety review has been conducted.

If the study is suspended or the decision is made not to proceed to the Main Cohort, a protocol amendment will be submitted to Health Authorities.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external

laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 variants (Alpha, Omicron BA.2, Omicron BA.4/5, and Omicron XBB.1.5), using validated pseudovirus neutralization assays. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152.

### 8.1.2 Participant-reported COVID-19 Symptoms

For participants in the Main Cohort, to determine the incidence of infection, study sites will contact all participants weekly (prior to Day 361) and then monthly (from Day 361) (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (adapted from the WHO COVID-19 case definition WHO 2022) from the past week. An Unscheduled Visit should be conducted if a participant reports any COVID-19-like symptoms. At the Unscheduled Visit, the Investigator should discuss all symptoms the participant is experiencing including those that are mild to determine if the participant meets the clinical criteria adapted from the WHO COVID-19 case definition for an Illness Visit. If the participant meets the case definition, the COVID-19 initial assessment is started.

The Investigator site will need to conduct Illness Visits within 3 days of the qualifying symptoms being reported (see Section 8.1.3 for more on Illness Visits). Participants who develop any symptoms that could be due to COVID-19 must be advised to contact the study site as soon as possible.

Illness Visits should only be initiated if a participant meets either of the following criteria adapted from the WHO COVID-19 case definition clinical criteria (WHO 2022):

- Any two of the following: fever*, cough, positive COVID-19 test (rapid antigen test or RT-PCR)

OR

- Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever*, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea,

nausea/diarrhea/anorexia, conjunctivitis, positive COVID-19 test, symptom as judged by the Investigator to be related to COVID-19

*Subjective definition to be used for fever.

Participants who present with COVID-19 qualifying symptoms after Visit 1 in the Main Cohort will be instructed to attend the study site for Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever [≥ 38°C], cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020.

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a

local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site illness visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

At IL-D1, the study site will set up an illness e-Diary on the participant's own cellphone or equivalent device. If a participant does not have a suitable device the study site will issue an Illness e-Diary device. The study site will train the participant on how and when to complete the e-Diary and document their daily symptoms. Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in the Illness e-Diary. The status of ongoing symptoms reported in the e-Diary at the end of an illness series will be recorded. The end date for any symptoms still present after 14 days will be documented in the eCRF. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

For the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants are to be encouraged to contact the site if their symptoms worsen.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as

detailed in the Laboratory Manual). Visit 5 (administration of the second dose of IMP) is only allowed to overlap with IL-D14. If Visit 5 is scheduled to occur at any of the other Illness Visit days, it should be delayed to IL-D14.

The Illness Visit assessment pathway may be initiated more than once (up to 10 times) for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories.

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of SARS-CoV-2 Spike protein mutations identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs, and any observations will be documented in the participant's medical records (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again 10 to 15 minutes after the second injection is given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse

oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Electrocardiograms

A single 12-lead ECGs will be performed at screening for the Sentinel Safety Cohort and Main Cohort (time points specified in the SoA; see Section 1.3). A 12-lead ECG will be obtained after 5 minutes' supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal, borderline, or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as unscheduled assessments.

All ECG readings will be digitally stored as source documents.

### 8.2.4 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort (see Section 1.3.1, Section 1.3.2, and Section 1.3.3).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea (or blood urea nitrogen) | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T oI (Main Cohort; screening only) |
| Glucose (random) | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) (or international normalized ratio) |
| **Other (women of childbearing potential only)** | |
| Urine serum (β-hCG) pregnancy test | Follicle stimulating hormone [a] |

[a] For female participants aged < 50 years who are considered postmenopausal, will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.

β-hCG = beta human chorionic gonadotropin; ULN = upper limit of normal.

For female participants aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts), and using a dipstick test at Visit 1 (both cohorts) and Visit 5 (Main Cohort only). For Visits 1 and 5, urine pregnancy test must be performed and be negative prior to dosing. This is especially important for any female participants who have not reached

menarche at enrollment into the study and whose child-bearing potential is expected to change during the study. A serum pregnancy test may be performed if a urine pregnancy test is not possible.

### 8.2.5 Other Safety Assessments

#### 8.2.5.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.5.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling may be recorded in the medical record at site visits.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after, 30 minutes (+ 10 minutes), and 1 hour after both injections are complete and also prior to participant release. Injection site reactions will also be monitored on Visit 2 (Day 3), Visit 3 (Day 5) and Visit 4 (Day 8) for the Sentinel Safety Cohort and Visit 2a (Day 8) and Visit 6 (Day 189) for the Main Cohort.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following each administration of study intervention. Adverse events occurring after 90 days following each study intervention administration and assessed by the Investigator as having a causal relationship to IMP and/or is COVID-19-related but does not prompt an Illness Visit (eg, asymptomatic COVID-19) will be collected in the eCRF. Serious adverse events, MAAEs, and AESIs will be collected throughout the study.

Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156, AZD3152, and AZD7442 in this study are based on those identified for EVUSHELD and are as follows:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoAs (Section 1.3).

Medically attended adverse events are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits (including Illness Visits themselves) will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE

within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156/AZD3152 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.10.1 Maternal Exposure

The IMP should not be given to pregnant women.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD3152, AZD5156, and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD3152 and AZD7442 from the Main Cohort, AZD5156 from the Sentinel Safety Cohort, and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156, AZD3152, and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, nasal lining fluid PK samples will be collected only for the first 600 participants (approximately). Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$;
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD1061, AZD3152, and AZD8895 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated bioanalytical methods. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, including additional SARS-CoV-2 nAb, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as

specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD3152.

For storage, re-use and destruction of biomarker samples see Section 8.5.

#### 8.6.2.1 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing peripheral blood mononuclear cells using methods that may include flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell

receptor sequencing, and other methodology as determined by the Sponsor. Samples will be collected at Illness Visit time points specified in the SoAs (Section 1.3). Additionally, plasma may be isolated from the whole blood samples collected to isolate peripheral blood mononuclear cells, which can be utilized for exploratory immunogenicity and biomarker analyses.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort.

## 9.1 Statistical Hypotheses

The primary efficacy objective is to compare AZD3152 to AZD7442 in the prevention of symptomatic COVID-19 observed up to 181 days after the participant's last dose. A superiority test will be performed to compare the hazard rate of symptomatic COVID-19 between treatment arms. The null hypothesis will be rejected if the HR 95% CI upper bound is less than 1.0 using a 2-sided test at a significance level of 5% ($\alpha = 0.05$). If the null hypothesis is rejected in favor of the alternative hypothesis, it will be concluded that the data provide evidence AZD3152 is superior to AZD7442 in preventing symptomatic COVID-19 during the study period. The hypotheses are as follows:

$$H_0: \frac{\lambda_{\mathrm{AZD3152}}}{\lambda_{\mathrm{AZD7442}}} \geq 1.0,$$

$$H_{\mathrm{A}}: \frac{\lambda_{\mathrm{AZD3152}}}{\lambda_{\mathrm{AZD7442}}} < 1.0,$$

where $\lambda_{\mathrm{AZD3152}}$ and $\lambda_{\mathrm{AZD7442}}$ are the instantaneous symptomatic COVID-19 hazard rate of AZD3152 and AZD7442, respectively.

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the Parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD3152 (plus placebo) or AZD7442.

The overall symptomatic COVID-19 blinded event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed.

The sample size in the Main Cohort is driven by the total number of events required to demonstrate the efficacy of AZD3152 versus AZD7442 in the prevention of symptomatic COVID-19. A target sample of approximately 3200 participants has been selected to reach the required number of events. Approximately 40 events will provide at least 90% power to demonstrate that the lower bound of the 2-sided 95% CI is less than 1, under the assumption that the annual event rate will be approximately 3.2% in the control arm, HR of 0.30 (70% efficacy), significance level of $\alpha = 0.05$, and 10% attrition. Assumptions are based on data from prior studies with AZD7442 and reported estimates of the event rate among those with immunocompromising conditions (Kelly et al 2022).

The Main Cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD3152 compared with 1600 participants receiving EVUSHELD within the study.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | These populations will consist of all randomized participants who received part or all of study intervention. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. Participants in the FAS will be classified according to the assigned treatment. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Anti-drug antibody analysis set | All safety analysis set participants with a non-missing baseline and at least one non-missing post-baseline ADA result of the mAb component(s) evaluated. AZD7442 and AZD5156 participants will be considered ADA-evaluable if either one or both of the respective mAb components includes a baseline and post-baseline result of the individual component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the indicated treatment classification in the corresponding analysis set population.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses. Methods for controlling multiplicity across endpoints will be presented in the Statistical Analysis Plan.

### 9.4.2 Efficacy

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops their first symptoms for COVID-19 at any time up to Visit 9 (Day 361). Positive cases require a central RT-PCR test and meet the qualifying symptoms as indicated by the Investigator satisfying the modified WHO definition of symptomatic COVID-19 (see Section 8.1.2). Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to compare prophylactic efficacy (ie, 1-HR) of AZD3152 versus AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Participants who become unblinded to treatment assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding or receipt of the first dose of COVID-19 preventive product. Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and will be included in the analysis. Participants who withdraw early from the study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

Other efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through

Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis of secondary efficacy endpoints.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by SARS-CoV-2 variant, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers with SARS-CoV-2 variants, including Alpha, Omicron BA.2, Omicron BA.4/5 and Omicron XBB.1.5 between treatment groups will be conducted using GMT ratio. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152. Analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

### 9.4.4 Anti-drug Antibody Variables

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed. Further details are provided in the SAP.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of the 2 component mAbs of AZD5156. The following single dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

## 9.5 Planned Analyses

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK concentrations at Day 29. The remaining two analyses will include all available data when conducted.

The study will maintain a double-blind period until approximately 40 or more participants have confirmed symptomatic COVID-19 to support the primary objective of efficacy and trigger the primary analysis. To maintain the integrity of the study for rigorous evaluation of safety and efficacy through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analyses will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan. Participant-level unblinding information will be kept strictly confidential, and the rationale for any unblinding will be documented. An additional interim analysis may be conducted to evaluate safety and PK of the second dose at Day 210. This analysis will only be conducted if the primary analysis has been previously conducted. The SAP will describe the planned analyses in greater detail.

If there is a medical need for AZD3152 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis and data readouts that may reveal treatment assignments if conducted prior to the primary analysis.

## 9.6 Safety Review Committee – Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort, as discussed in Section 4.1.1.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but

are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

## C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
   (a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   (a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   (b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 13, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care.

# Appendix F List of Immunosuppressive Medications

The list of immunosuppressive medications in the table below is not exhaustive.

| **1. Alkylating Agents** | | | |
|---|---|---|---|
| Bendamustine | | Melphalan | |
| Busulfan | | Mitomycin | |
| Carboplatin | | Oxaliplatin | |
| Carmustine | | Procarbazine | |
| Cisplatin | | Streptozocin | |
| Cyclophosphamide | | Temozolomide | |
| Dacarbazine | | Thiotepa | |
| Ifosfamide | | Trabectedin | |
| Lomustine | | | |
| **2. Selective Immunosuppressants** | | | |
| General | | Calcineurin Inhibitors | Antimetabolites |
| Azathioprine | Lenalidomide | Cyclosporine | Methotrexate |
| Belumosudil | Mycophenolate | Tacrolimus | Nelarabine |
| Bortezomib | Pomalidomide | Voclosporin | Pemetrexed |
| Cladribine | Teriflunomide | | Pralatrexate |
| Dimethyl fumarate | Thalidomide | | Irinotecan |
| Diroximal fumarate | Anti-thymocyte immunoglobulin (horse, rabbit) | | Liposome |
| Leflunomide | | | Capecitabine |
| | | | Clofarabine |
| | | | Cytarabine |
| | | | Decitabine |
| | | | Floxuridine |
| | | | Fludarabine |
| | | | Fluorouracil |
| | | | Gemcitabine |
| | | | Mercaptopurine |
| JAK Inhibitors | | mTOR Inhibitors | Sphingosine-1-phosphate Receptor Modulators |
| Baricitinib | | Everolimus | Fingolimod |
| Tofacitinib | | Sirolimus | Ozanimod |
| Upadacitinib | | | Ponesimod |
| Peficitinib | | | Siponimod |
| Itacitinib | | | |
| **3. Monoclonal Antibodies** | | | |
| General | | Anti-IFN | Anti-CD20 |
| Alemtuzumab (anti-CD52) | | Anifrolumab | Ibritumomab |
| Belimumab | | Emapalumab | Obinutuzumab |
| Begelomab (anti DPP-4/CD26) | | | Rituximab |
| Teprotumumab (anti-IGF-1) | | | Ocrelizumab |
| Inebilizumab (anti-CD19) | | | Ofatumumab |
| Muromonab (anti-CD3) | | | |
| Inotuzumab Ozogamicin (anti-CD22) | | | |

| Selective T-Cell Costimulation Blockers | Integrin Receptor Agonists | Bruton Tyrosine Kinase Inhibitors | |
|---|---|---|---|
| Abatacept<br>Belatacept | Natalizumab<br>Vedolizumab | Ibrutinib<br>Acalabrutinib<br>Pirtobrutinib | Zanubrutinib<br>Deucravacitinib |
| Complement Inhibitors | TNF-alpha Inhibitors | IL-23 Inhibitors | |
| Pegcetacoplan<br>Eculizumab (anti-C5)<br>Ravulizumab (anti-C5)<br>Sutimlimab (anti-C1) | Adalimumab<br>Afelimomab<br>Certolizumab Pegol<br>Etanercept<br>Golimumab<br>Infliximab | Ustekinumab<br>Guselkumab<br>Tildrakizumab<br>Risankizumab | |
| IL-17 Inhibitors | IL-1 Inhibitors | IL Inhibitors (other) | |
| Secukinumab<br>Ixekizumab<br>Bimekizumab<br>Brodalumab<br>Netakimab | Anakinra<br>Canakinumab<br>Rilonacept | Basilximab (anti IL-2)<br>Sarilumab (anti IL-6)<br>Satralizumab (anti IL-6)<br>Siltuximab (anti IL-6)<br>Tocilizumab (anti IL-6)<br>Spesolimab (anti IL-36) | |
| **4. Steroids** | | | |
| Dexamethasone: ≥ 3 mg per day, minimum of 2 weeks of therapy<br>Prednisolone: ≥ 20 mg per day, minimum of 2 weeks of therapy<br>Prednisone: ≥ 20 mg per day, minimum of 2 weeks of therapy | | | |

CD = cluster of differentiation; DPP = dipeptidyl peptidase; IFN = interferon; IFG = insulin-like growth factor; IL = interleukin; TNF = tumor necrosis factor.

# Appendix G Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 5.0 [07 February 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| TITLE PAGE | The study intervention has been changed from 'AZD5156' to 'AZD5156/AZD3152' and a similar change has been made to the study title | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy, although AZD5156 will still be studied in the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of follicle stimulating hormone at screening | Required for eligibility criteria |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples have been removed from Day 271 and the EDV | Rationalization of blood sampling to reduce invasive procedures |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 2.1 Study Rationale | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.3 Benefit/Risk Assessment | Section updated throughout to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and overall benefit/risk conclusion aligned with Investigator's Brochure. | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy; also text aligned with Investigator's Brochure |
| 3 OBJECTIVES AND ENDPOINTS | Created separate primary and secondary objectives and endpoints for the Sentinel Safety and Main Cohorts | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.1 Overall Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.2 Main Cohort | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2 Scientific Rationale for Study Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | New section | Justification as to why AZD7442 is considered a better choice of control than placebo |
| 4.3.2 Justification for AZD3152 Dose | New section | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #10, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #21, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, any alkylating agents will qualify as a risk factor, not just high-dose agents | Low-dose cyclophosphamide is used as immunotherapy in lymphoma, breast and ovarian cancer |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, a moderate or severe secondary immunodeficiency will now qualify as a risk factor | To broaden the study population |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #11, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #13, noted that concurrent participation in another interventional study where the participant ceased IMP treatment >90 days who is in the follow-up period of the study and not expected to receive further IMP is permitted for inclusion | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #17, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.1 Study Intervention(s) Administered | The whole section (including the table) has been updated to reflect the use of AZD3152 as a standalone therapy in the Main Cohort, including use of placebo to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.5 Concomitant Therapy | Added more details regarding permitted concomitant medications for the Sentinel Safety Cohort and clarified the wording around SARS-CoV-2 vaccines and COVID-19 antivirals | Clarification |
| 8.5.1.1 Determination of Drug Concentration | Serum PK samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 8.5.2.1 Anti-drug Antibody Assessments | Samples for determination of ADA will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 9.1 Statistical Hypotheses | The whole section has been updated to reflect the use of AZD3152 as a standalone therapy | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.2 Sample Size Determination | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156; minor adjustments made to wording of sample size determination | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Schema updated in line with applicable changes from the protocol text | Schema made consistent with amended text |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Timing of Day 1 urine pregnancy test changed from 'prior to randomization' to 'predose' and footnote updated to clarify test must be on same day as dosing | Consistency with other parts of the table |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Clarified that laboratory safety samples on Day 1 will be taken predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Noted that duration of recording daily symptoms associated with COVID-19 will be 14 days | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 4.1 Overall Design | Wording regarding qualification for Illness Visits has been updated | Clarification |
| 4.1.1 Sentinel Safety Cohort | Added justification for use of AZD5156 safety data to initiate dosing with AZD3152 in the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.1 Rationale for Administration Site | Removed reference to components of the study interventions being monoclonal antibodies | One injection for those assigned to AZD3152 will be placebo |
| 4.2.2 Rationale for Study Population | Changed references to AZD5156 to AZD3152 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.3.1 Justification for AZD5156 Dose | Noted that AZD5156 will be administered in the Sentinel Safety Cohort | Clarification |
| 4.3.4 Justification for Placebo | Added details of administration of placebo that will be included with AZD3152 to maintain the blind | One injection for those assigned to AZD3152 will be placebo |
| 4.4 End of Study Definition | Noted that results from some laboratory samples may not become available until after the study completion date | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | AZD3152 is now included | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.1 Randomization | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.2 Blinding | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.2 Blinding | Added AstraZeneca Bioanalytical monitor and unblinded Biometric teams to the list of those who will have access to the randomization list during the study | Clarification |
| 7.1 Discontinuation of Study Intervention | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort, also added clarification about process if participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Noted that AstraZeneca will make the final decision on a temporary hold after analysis of the safety data | Clarification |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Clarified that study would be put on temporary hold if Grade 3 or higher AEs were reported for at least 2 participants (and not simply when 2 Grade 3 or higher AEs were reported) | Wording made consistent with previous AZD7442 studies |
| 8.2.2 Vital Signs | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed) | Clarification regarding the time around vital signs collection |
| 8.2.4 Clinical Safety Laboratory Assessments | Removed reference to Laboratory Manual | Not applicable |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that glucose assessment is specifically glucose (random), and added pregnancy test and FSH to the table of variables | Clarification |
| 8.2.4 Clinical Safety Laboratory Assessments | Added clarifications around pregnancy testing. Furthermore, the FSH evaluation no longer applies only to those in the Sentinel Safety Cohort. | Clarification |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Reiterated that SAEs, MAAEs, and AESIs will be collected throughout the study | Clarification |
| 8.3.4 Adverse Events of Special Interest | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.3.9 Reporting of Serious Adverse Events | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.1 Pharmacokinetics | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.2.1 Anti-drug Antibody Assessments | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.6.2 Other Study-Related Biomarker Research | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.1 General Considerations | Description of study updated to reflect change of strategy in terms of using AZD3152 alone | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.2 Efficacy | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.6 Pharmacokinetics | Order of paragraphs reversed, so that Sentinel Safety Cohort is discussed first, text regarding Main Cohort updated to reference AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Removed text regarding an emerging VOC significantly affecting the neutralization activity of AZD7442 | Updated information, as there is a possibility that the situation described in the deleted text may have already occurred |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.7 Data Safety Monitoring Board – Main Cohort | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

**CSP Version 4.0 [16 January 2023]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to add efficacy as a secondary endpoint to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the Main Cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy of AZD5156 compared with AZD7442. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

The protocol has also been amended to enhance the safety assessments of the Main Cohort, at the request of a Regulatory Authority.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1; noted that the test must return a negative result before dosing | To align with internal guidance for WOCBP |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total) |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Additional assessments of vital signs have been added on Days 8 and 189 of the Main Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Pregnancy test added at Visit 1, with the timing specified as prior to randomization | To align with internal guidance for WOCBP (pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Sample for serum chemistry, hematology, coagulation (local laboratory) will be collected on Days 1, 8, and 29; noted that this assessment is to be performed for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of troponin at screening for the Main Cohort | To increase cardiac safety monitoring |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added the footnote clarifying that home or mobile visits by study staff may substitute for site visits to the Day 1 Illness Visit as well | To ensure sites can perform the Day 1 Illness Visit at home, if needed |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e-Diary and training has been added, along with Investigator site review of e-Diary entry completion | Clarification and for consistency |
| 3 Objectives and Endpoints | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP administration (was previously to Day 29) | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention |
| 3 Objectives and Endpoints | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3 Objectives and Endpoints | References to dominant variants removed | To make the objectives/endpoints less specific |
| 3 Objectives and Endpoints | nAb responses to variant BA.2 will be evaluated | To include current and emerging variants of concern |
| 3 Objectives and Endpoints | Addition of secondary endpoint related to efficacy | Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case will be evaluated as a secondary endpoint |
| 3 Objectives and Endpoints | For the objective '*To characterize the cellular immune responses to SARS-CoV-2*' the following endpoint has been added: *Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing* | To further characterize the cellular immune response |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated. This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total) |
| 4.1 Overall Design | The collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 4.1 Overall Design | Noted that MAAEs will be collected throughout the study | Consistent with added safety endpoint |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #4 has been deleted | Duplication with the original inclusion #7 |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11 (original exclusion #10), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15 (original exclusion #14), hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #3 (original inclusion #4) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on negative rapid antigen test at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #4 (original inclusion #5) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Text regarding participants with cancer in Inclusion #5 (original inclusion #6) has been updated to clarify that those with solid tumor cancer who are included in the study must be on active treatment, excluding the exceptions noted; hematologic malignancy has now been noted as a separate risk factor | This was a Regulatory Authority request |
| 5.2.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12 (original exclusion #11), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Subsection on stopping rules for Main Cohort removed | Replaced with new section on Study Suspension/Early Termination |
| 7.4 Study Suspension/Early Termination | New section | Added for consistency with wording used in AZD7442 studies |
| 8.2.3 Electrocardiograms | New section | Added to describe procedures for ECG |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted that serum chemistry, hematology, coagulation (local laboratory) assessments will be conducted for at least the first 600 participants in the Main Cohort; deleted text stating that clinical safety laboratory assessments will not routinely be performed for the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted (in Table 11) that troponin assessment will be performed in the Main Cohort at screening | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1.1 Determination of Drug Concentration | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.6.2.1 Assessment of Cell-mediated Immune Responses | New section | For consistency with endpoints section |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.7 Data Safety Monitoring Board – Main Cohort | Added MAAEs to the safety parameters that will be assessed as part of the DSMB review | Consistent with MAAEs having been added as a safety endpoint |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Updated footnote to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 1.3 Schedule of Activities | Updated text describing the duration of treatment and follow-up periods from 12 months to 15 months | To reflect the change to the study design to increase the safety collection time |
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Moved the footnote marker for vital signs assessments from dosing days to the overall row header as abnormal vital signs must be repeated at all scheduled vital signs assessments, and not only on dosing days, after the participant has been at rest for at least 5 minutes | Correction for consistency with vital signs assessments for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The numbers of confirmed cases and deaths due to COVID-19 have been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'currently circulating Omicron variants' has been replaced with 'past Omicron variants' | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Specified that cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies | Clarification that these events will be monitored in other AZD5156 studies in addition to the present study |
| 2.3.2 Benefit Assessment | Noted that similarity of AZD5156 to AZD7442 is in terms of structure and mechanism of action | Clarification |
| 2.3.2 Benefit Assessment | Noted that AZD7442 and AZD5156 may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus | Clarification |
| 3 Objectives and Endpoints | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative RT-PCR at baseline to positive at any time up to 6 and 12 months | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 3 Objectives and Endpoints | Minor change to endpoint describing how exploratory samples may be used to align with change in Section 8.5.2.3 | Clarification |
| 4.1 Overall Design | Added that the safety and neutralizing activity of AZD5156 will be compared with AZD7442 for pre-exposure prophylaxis of | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | COVID-19 and that the study will be conducted globally | |
| 4.1 Overall Design | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.1 Overall Design | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1 Overall Design | Added that immediate AEs will be collected for a 1-hour observation period after study intervention administration | Clarification |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Updated text to provide further information on ESDRs | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.2 Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.2 Scientific Rationale for Study Design | Noted that a dose exploration study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.1 Rationale for Administration Site | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions | To further clarify rationale for the administration site |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the threshold (was $IC_{90}$ now $IC_{80}$) | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.1 Inclusion Criteria (Sentinel) | For inclusion #6, clarified that participant must understand and comply with all study requirements/procedures | Clarification |
| 5.2.1 Inclusion Criteria (Main) | For inclusion #7, clarified that participant must understand and comply with all study requirements/procedures (including those at Illness Visits) | Clarification |
| 5.4 Screen Failures | Criteria for rescreening have been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated in the text and in a footnote to Table 8 | Updated to reflect current information |
| 6.1 Study Intervention(s) Administered | Noted in the text and in a footnote to Table 8 that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive the first component of their assigned intervention will all receive the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Added specific details for placebo | Clarification |
| 6.1 Study Intervention(s) Administered | Noted in Table 8 that L-histidine hydrochloride is monohydrate | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage and administration of IMP | Wording added to provide more comprehensive details of IMP storage and administration |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.1 Randomization | Added text that participants will receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention, and those having access to the randomization list during the study | Clarification |
| 6.3.2 Blinding | Removed text about Investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.5 Concomitant Therapy | Minor update to wording regarding the Concomitant Medication eCRF | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the 'Restricted' section in Table 9 | To ensure the correct patient population is enrolled |
| 8 Study Assessments and Procedures | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 8.1.2 Participant-reported COVID-19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | Extra information added regarding e-Diaries and documentation in the eCRF | Updated for clarity |
| 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments | Added text stating that genotypic sequencing analysis and phenotypic characterization would be of SARS-CoV-2 Spike protein mutations rather than of the virus | Clarification |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment, and noted that any observations will | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | be documented in the participant's medical records | |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 8.2.4 Clinical Safety Laboratory Assessments | Included the option for urea results to be reported as blood urea nitrogen, and for prothrombin time results to be reported as international normalized ratio | Clarification |
| 8.2.5.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.5.2 Injection Site Reactions | Noted that diameters of any redness/swelling may be recorded at site visits | Clarification |
| 8.2.5.2 Injection Site Reactions | Removed references to specific time points for the Sentinel Safety Cohort | Those specific details were not needed because reference is made to the SoAs |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Noted that AESIs will be programmatically identified through AE information that is collected in the eCRF | Clarification |
| 8.3.4 Adverse Events of Special Interest | Minor edits made throughout the section | Updated for clarity |
| 8.3.9 Reporting of Serious Adverse Events | Minor change to wording of statement about reporting of SAEs | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.3.11.1 Timelines | Updated wording for SAEs associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.2.3 Additional Serum Immunogenicity | Minor change to statement regarding how exploratory serum samples may be used | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.3 Populations for Analyses | Updated the definition of the SARS-CoV-2 neutralizing antibody analysis set to remove the text 'with quantifiable SARS-CoV-2 serum titers' | This was a Regulatory Authority request related to the inclusion of participants without quantifiable serum titers but who received investigational product |
| 9.3 Populations for Analyses | Updated the definition of the anti-drug antibody analysis set | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.1 General Considerations | Noted that details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses | Clarification |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.4.2 Efficacy | Deleted reference to 'incidence of post treatment COVID-19' as 'incidence of post treatment symptomatic COVID-19' is already specified | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 9.4.4 Anti-drug Antibody Variables | Text regarding anti-drug antibody variables edited, with a reference added to the SAP | To simplify the text to keep the necessary information and refer to the SAP for further details |
| 9.5 Planned Analyses | Added details of analyses for Sentinel Safety Cohort | Clarification |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | team will remain blinded during primary analysis | |
| 9.5 Planned Analyses | Noted that an evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID 19 be observed prior to the final analysis | Clarification |
| 9.7 Data Safety Monitoring Board – Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore, have not been summarized |

**CSP Version 3.0 [09 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort, at the request of a Regulatory Authority.

**Summary of Changes**:

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory | This has been added to assist with making a decision regarding whether a female participant is |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | assessments at screening for the Sentinel Safety Cohort | postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination, vital signs, and injection site reaction monitoring (local reactogenicity) have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Sample for clinical safety laboratory assessments added at Day 1 (predose) for the Sentinel Safety Cohort | To obtain baseline values |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For the vital signs assessment on Day 1 of the Sentinel Safety Cohort, the indicator '(predose)' has been deleted | This has been deleted for reasons of clarity, because Day 1 vital signs are not only assessed predose, and the existing footnote (a) provides specific details of the timings |

**CSP Version 2.0 [02 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

Note: due to a typing error, the word 'imitating' appears several times instead of 'initiating' in this historical Summary of Changes, and reference is made to the fact that '*no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed*'; this should have read 80 adult Main Cohort participants.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version Number: 7.0

Study Intervention:

*Sentinel Safety Cohort*
AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152), or placebo (0.9% sodium chloride for injection)

*Main Cohort*
AZD3152 monoclonal antibody or placebo (0.9% sodium chloride for injection)

*Sub-study*
AZD3152 monoclonal antibody or AZD7442 (EVUSHELD), the active comparator

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Brief Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 7.0 | 14-Jun-2023 |
| CSP Version 6.0 | 24-May-2023 |
| CSP Version 5.0 | 07-Feb-2023 |
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| CSP Version 3.0 | 09-Dec-2022 |
| CSP Version 2.0 | 02-Dec-2022 |
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### CSP Version 7.0 [14 June 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended primarily to change the comparator for the Main Cohort from (active) EVUSHELD to placebo. This change was initiated as the Parent study is now primarily an efficacy and safety study.

A summary of changes is presented below. Where applicable, the changes were also applied to the synopsis.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global change | For the Main Cohort, the comparator has been changed from (active) EVUSHELD to placebo. As placebo comparator will be given as a single injection (whereas EVUSHELD required two injections) at each dosing occasion, the injection of matching placebo that was part of the blinded AZD3152 administration has been removed | Change made in response to Health Authority feedback |
| Global change | "AZD7442" has been changed to "EVUSHELD" throughout except in places where AZD7442 would be more appropriate (eg, PK) | Clarification of the name for the comparator |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.5.1.1 Determination of Drug Concentration<br>8.5.2.1 Anti-drug Antibody Assessments | Serum PK and ADA/nAb samples will now be collected and analyzed only for the first 1200 participants (approximately) in the Main Cohort, although serum samples will still be collected from all participants for potential future analyses | It is anticipated that data from 1200 participants should be sufficient for the purposes of these analyses, but serum samples will also be collected from the other participants for potential future analyses. |
| 2.1 Study Rationale<br>4.1 Overall Design | Added justification for change of comparator to placebo, and also describe the three possible combinations of comparator that a Main Cohort Participant could receive | Justification required due to the change of comparator |
| 4.2.3 Rationale for Use of Placebo as Comparator for the Main Cohort | Section has been reconfigured to show rationale for use of placebo as comparator (not AZD7442) | Update because of change of comparator |

| | | |
|---|---|---|
| 5.2.1 Inclusion Criteria | Updated Inclusion criterion #5 to include advanced or untreated HIV infection (people with HIV and history of CD4 cell counts < 200/mm$^3$ within 6 months of Visit 1, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) | Immunobridging endpoint was removed and the SARS-CoV-2 nAb analysis is now a descriptive analysis; therefore, there is flexibility to include advanced and untreated HIV participants (for some of which we may not be able to determine the SARS-CoV-2 nAb titers in the lentivirus based pseudovirus assay) to the immunocompromised population |
| 5.2.2 Exclusion Criteria | Removed (previous) Exclusion criterion #7 (Has HIV infection) | Immunobridging endpoint was removed and the SARS-CoV-2 nAb analysis is now a descriptive analysis; therefore, there is flexibility to include advanced and untreated HIV participants (for some of which we may not be able to determine the SARS-CoV-2 nAb titers in the lentivirus based pseudovirus assay) to the immunocompromised population |
| 8.5.1.1 Determination of Drug Concentration | Serum PK samples will now be collected and analyzed only for the first 1200 participants (approximately) in the Main Cohort, although serum samples will still be collected from all participants for potential future analyses. Samples from participants who receive placebo will be analyzed if required. | It is anticipated that data from 1200 participants should be sufficient for the purposes of these analyses, but serum samples will also be collected from the other participants for potential future analyses. |
| 8.5.2.1 Anti-drug Antibody Assessments | Samples for determination of ADA will now be collected and analyzed only for the first 1200 participants (approximately) in the Main Cohort, although serum samples will still be collected from all participants for potential future analyses. Samples from participants who receive placebo will be analyzed if required. | It is anticipated that data from 1200 participants should be sufficient for the purposes of these analyses, but serum samples will also be collected from the other participants for potential future analyses. |
| 9 STATISTICAL CONSIDERATIONS | Added details of the combined comparator study arm for the efficacy evaluation | Some participants in the Main Cohort will have received EVUSHELD (prior to CSP v7.0) as comparator while others (as of CSP v7.0) will receive placebo |

| | | |
|---|---|---|
| 9.5 Planned Analyses | Noted that primary analysis will only be conducted once median follow-up time is greater than 181 days in the full analysis set | Clarified the timing of the analysis |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global change | When discussing the present study, the word 'control' has been substituted with 'comparator' | More appropriate language is now used considering the switch from AZD7442 to placebo as comparator |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.2.4 Clinical Safety Laboratory Assessments | Minor change to language: pregnancy tests will be done locally (not specifically at a local laboratory) | Clarification, as tests may be performed at the clinic |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added footnote to allow the screening troponin test to be performed on Day 1 (predose) and noted in the table that this assessment will be done using a local laboratory | Reflection of clinical practice |
| 2.1 Study Rationale<br>4.1 Overall Design | Noted that the sub-study will be Phase II | Clarification |
| 2.1 Study Rationale | Noted that the sub-study will be described in an addendum. | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |
| 2.2.2 AZD5156, AZD3152, and EVUSHELD | Removed reference to "the ongoing pandemic" | Updated to reflect the decline in COVID-19 incidence |
| 3 OBJECTIVES AND ENDPOINTS | Clarified time of adverse event assessments | Clarification |
| 4.3 Justification for Dose | Removed sub-section "Justification for AZD7442 Dose" | Comparator is now placebo for the Main Cohort |
| 5.2.1 Inclusion Criteria | For inclusion criterion #5, the bullet point regarding moderate or severe primary or secondary immunodeficiency has been reworded. | Reworded for clarity/readability |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5 | Noted that requirement for negative pregnancy test was only for WOCBP, that participants can wait up to 14 days to comply with criteria #5 or #6, and that instructions for participants who are not eligible for the second dose (Visit 5) are in Section 7.1. | Clarifications |
| 6.5 Concomitant Therapy | In the table, the timeline for COVID-19 antivirals has been reworded for clarity | Clarification |
| 8.2.1 Physical Examinations | Each clinically significant abnormal finding from the time of study intervention administration (was previously following randomization) should be reported as an AE | Timeframe updated for consistency with AE collection period noted in Section 8.3.1 |
| 9.4.5 Safety | Noted that the most recent version of MedDRA will only be used where possible | Contingency, as it may not always be possible to use the latest version |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| FAS | Full analysis set |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |

| Abbreviation or special term | Explanation |
|---|---|
| GCP | Good Clinical Practice |
| GMFR | Geometric Mean Fold Rise |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| hCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{50}$ | Concentration giving half-maximal inhibition |
| $IC_{80}$ | Concentration required for 80% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IVIG | Intravenous immunoglobulins |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |

| Abbreviation or special term | Explanation |
|---|---|
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SCIG | Subcutaneous immunoglobulins |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study. The main part of this CSP refers to the parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum to the CSP.

In the Parent study, the Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442 (EVUSHELD)] and AZD3152) in healthy adults and the Phase III Main Cohort will assess the safety, efficacy, PK, and neutralizing activity of two doses of AZD3152 compared with two doses of comparator given at a 6-month interval in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19.

Prior to CSP v7.0, the comparator for the Main Cohort was EVUSHELD as the immunobridging portion of the study was incorporated into the Parent study. At the request of regulatory authorities, a sub-study specifically for immunobridging is being undertaken (which will be conducted in the US only). As a result, the Parent study will become an efficacy and safety study, and the comparator will therefore be changed to placebo. As the comparator is given on two occasions, this means that a participant randomized to the comparator arm may receive (a) two doses of EVUSHELD, (b) a dose of EVUSHELD and a dose of placebo, or (c) two doses of placebo.

The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and EVUSHELD.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through approximately 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA to AZD5156, AZD3152, and AZD1061, ADA titers |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and EVUSHELD and/or placebo | Occurrence of AEs collected through approximately 90 days after each IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus EVUSHELD and/or placebo) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and EVUSHELD and/or placebo administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study that will be conducted in approximately 3706 participants (approximately 3256 in the Parent study and 450 in the sub-study) to evaluate the safety, efficacy, PK, and neutralizing activity of AZD3152 compared with EVUSHELD or placebo for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum.

The Parent study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with placebo.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (ie, active treatment or comparator) 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and EVUSHELD use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded to study intervention).

**Number of Participants:**

Approximately 3256 participants will be randomized in the Parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be

randomized 1:1 to receive AZD3152 or comparator.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: 1 dose of AZD3152 300 mg IM or comparator (on 2 occasions with a 6-month interval).

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Sentinel Safety Cohort as follows: after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b), and subsequently after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 subcohorts, prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

**Statistical Methods**

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK

concentrations at Day 29. The remaining two analyses will include all available data when conducted. The primary analysis for the Main Cohort will be conducted by a limited unblinded team after approximately 40 or more participants have met conditions for the primary efficacy endpoint and a median follow-up time of 181 days or more is observed.

Participants randomized to the comparator arm in the Main Cohort may have received doses of EVUSHELD or placebo at either first or second IMP administration and will be presented as a combined comparator study arm for the efficacy evaluation. Safety data will be summarized by each comparator group (EVUSHELD or placebo) separately and combined. When appropriate, actual dose(s) received may be presented separately to the combined comparator group. Any participant who received or was assigned to EVUSHELD at the first or second IMP dose will be presented as having received or been assigned to EVUSHELD. The SAP will provide details on the presentation of data by assigned and actual treatments received.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD3152 and comparator and to compare the efficacy of AZD3152 versus comparator in the Main Cohort for the prevention of symptomatic COVID-19. Separately, safety and PK of AZD5156 will be evaluated in the Sentinel Safety Cohort.

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops their first symptoms for COVID-19 at any time up to Visit 9 (Day 361). Positive cases require a central RT-PCR test and meet the qualifying symptoms as indicated by the Investigator satisfying the modified WHO definition of symptomatic COVID-19. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to compare prophylactic efficacy (ie, 1-HR) of AZD3152 versus comparator.

Adverse events and SAEs will be coded using the most recent version of MedDRA, where possible, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

<u>Efficacy Endpoints</u>

Other COVID-19 efficacy endpoints are derived as a binary outcome where each participant is

to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis of secondary efficacy endpoints.

SARS-CoV-2 nAb Response

The secondary endpoints of nAb responses against SARS-CoV-2 variants, including Alpha, Omicron BA.2, Omicron BA.4/5 and Omicron XBB.1.5 will be evaluated using the geometric mean titer (GMT) ratio between treatment arms. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152.

Characterization of PK

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of these 2 component mAbs of AZD5156. The following single dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or EVUSHELD, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

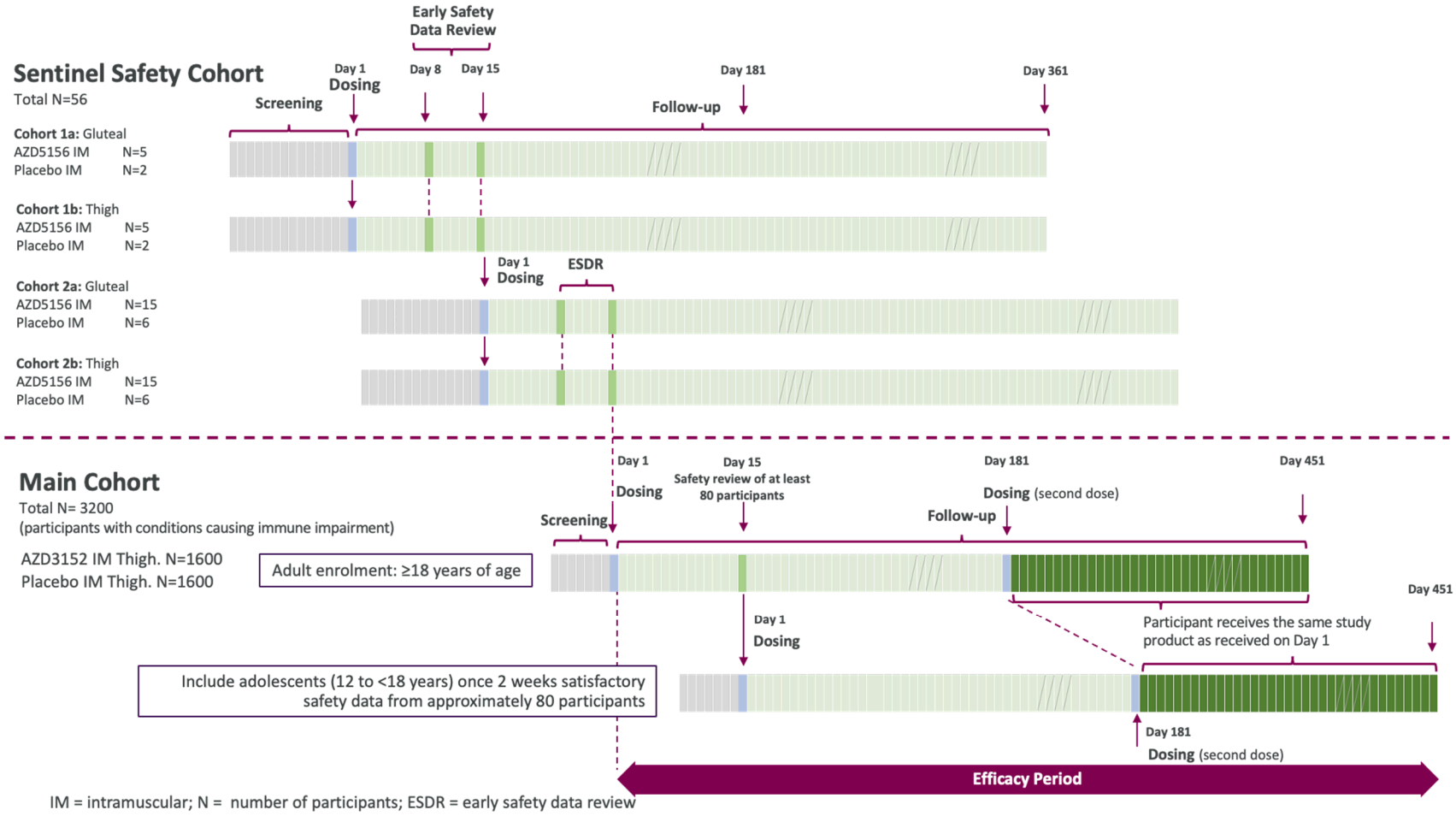
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort (data up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b), and then prior to enrollment of the Main Cohort.
Note: Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 14 days (Day -14 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| 12-Lead electrocardiogram (single, to be performed locally) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [f] | X | X | X | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | | | | | | | |
| Verify selected eligibility criteria for receipt of second dose (Visit 5) [c] | | | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | Weight only (predose) | | | | | | X [d] |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [e] | X | X | X | | | | X | X | | | | | |
| 12-lead electrocardiogram (single, to be performed locally) | X | | | | | | | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Urine or serum β-hCG pregnancy test (WOCBP only, performed locally) [f] | X | X (predose) | | | | | X (predose) | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [g] | | X (predose) | | | | | X [h] (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [i] (predose) | | | | | X [i] (predose) | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) [j] | | X (predose) | X | | X | | | | | | | | |
| Troponin T or I (local laboratory) | X [k] | | | | | | | | | | | | |
| Follicle stimulating hormone [l] | X | | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [l] | | X ← → | | | | | | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Monthly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [m] | | | | | | | | | | | ◄——► | | |
| Assessment of AEs [n] | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |
| PK serum sample [o,p] | | X (predose) | | | X | X | X (predose) | X | X | | X | | |
| PK nasal lining fluid sample [q] | | X (predose) | | | X | X | | | | | | | |
| ADA and antidrug nAbs assessment serum sample [o] | | X (predose) | | | X | X | X (predose) | | X | | X | | |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample [r] | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |

## Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [s] | X | | | | X [s] | X | | | | | |
| Immediate AEs [t] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] See Section 5.2.3 for the eligibility criteria for the receipt of the second dose of study intervention at Visit 5.
[d] Excludes height measurement in adults aged 18 years and older.
[e] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[f] Sample urine or serum β-hCG pregnancy test must return a negative result before dosing. Pregnancy testing prior to each dose must be on the same day as dosing and is especially important for female participants who had not reached menarche on enrollment into the study.
[g] Sites will be provided with rapid antigen tests.
[h] If a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3).
[i] To be collected at baseline. The results are not needed prior to dosing.
[j] To be performed for at least the first 600 participants in the Main Cohort.
[k] It is acceptable for this to be performed on Day 1 (predose).
[l] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[m] Weekly (prior to Day 361) and then monthly (from Day 361) contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The weekly and monthly telephone calls should be performed in addition to any scheduled site visits.
[n] Adverse events that occur outside of the 90-day window between each study intervention administration that are either related to IMP, or are COVID-19-related but do not prompt an Illness Visit (eg, asymptomatic COVID-19), will be reported on the AE CRF page.
[o] Samples will only be collected and analyzed for the first 1200 participants (approximately) in the Main Cohort.
[p] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.

[q] Samples collected only for the first 600 participants (approximately) in the Main Cohort.
[r] Samples will be prioritized for PK and ADA/nAb analysis as needed
[s] Perform immediately, 30 minutes (+ 10 minutes) and 1 hour after both injections are complete, and prior to participant release.
[t] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; β-hCG = beta human chorionic gonadotropin; CRF = case report form; EDV = Early Discontinuation Visit; IMP = investigational medicinal product; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Unscheduled Visit** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|---|
| **Day [c]** | | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **+ 2** |
| Verify qualifying clinical symptoms [d] | X | | | | | | |
| Medical history | | X | | | X | | X |
| Targeted physical examination | | X | | | X | | X |
| Vital signs (including pulse oximetry) | | X | | | X | | X |
| Set up of e-Diary and training | | X | | | | | |
| Assessment of AEs, SAEs, MAAEs, and AESIs | | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily for 14 days by participant in Illness e-Diary) | | X ← → | | | | | |
| Investigator site review of e-Diary entry completion | | X (ongoing) | | | | | |
| Saliva sample for viral shedding | | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | | X | | | X | | X |
| PBMCs for T-cell responses | | X | | | X | | X |
| PK serum sample | | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Unscheduled Visit** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|---|
| **Day [c]** | | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **+ 2** |
| SARS-CoV-2 neutralizing antibody serum sample | | X | | | X | | X |
| Exploratory analysis serum sample | | X | | | X | | X |
| Telephone contact for safety monitoring [f] | | | X | X | | X | |
| WHO Clinical Progression Scale [f] | | X | X | X | X | X | X |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] If the participant meets the clinical criteria adapted from the WHO COVID-19 case definition (see Section 8.1.2), then an illness visit (IL-D1) will be initiated.

[e] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results may not be reported to sites during the Illness Visit period.

[f] For the duration of the Illness Visit period, sites should follow up with the participant either at the site visit or by telephone for home visits to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19.

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study. The main part of this CSP refers to the parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum to the CSP.

In the Parent study, the Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442 (EVUSHELD)] and AZD3152) in healthy adults and the Phase III Main Cohort will assess the safety, efficacy, PK, and neutralizing activity of two doses of AZD3152 compared with two doses of comparator given at a 6-month interval in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19.

Prior to CSP v7.0, the comparator for the Main Cohort was EVUSHELD as the immunobridging portion of the study was incorporated into the Parent study. At the request of regulatory authorities, a sub-study specifically for immunobridging is being undertaken (which will be conducted in the US only). As a result, the Parent study will become an efficacy and safety study, and the comparator will therefore be changed to placebo. As the comparator is given on two occasions, this means that a participant randomized to the comparator arm may receive (a) two doses of EVUSHELD, (b) a dose of EVUSHELD and a dose of placebo, or (c) two doses of placebo.

The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and EVUSHELD. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of COVID-19 that, as of 31 May 2023, has caused over 767 million confirmed cases of COVID-19, including more than 6.9 million deaths, reported to the WHO (WHO 2023). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated continued development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 AZD5156, AZD3152, and EVUSHELD

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including EVUSHELD. The potency of EVUSHELD was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against some of the more recent Omicron variants such as BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the

prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease. AZD3152 was initially developed to provide efficacy similar to that of EVUSHELD but with greater breadth against variants not potently neutralized by EVUSHELD.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of EVUSHELD with greater neutralization potency against the past Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to EVUSHELD, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156 was anticipated to have potent in vitro neutralization activity for all known current and past VOCs.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of EVUSHELD in vitro. Given both AZD3152 and EVUSHELD target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD3152 builds upon the established safety and efficacy of EVUSHELD. AZD3152 is expected to have a similar safety and PK profile and broader efficacy against a wider range of SARS-CoV-2 VOCs than EVUSHELD.

It is considered reasonable that AZD3152 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD3152 are similar to those of the component mAbs of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, BF.7, XBB, and XBB.1 for AZD3152 are superior to those of AZD7442.
- EVUSHELD has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725)

study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD3152 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD3152 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 and AZD3152 are provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with EVUSHELD, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the EVUSHELD mAb combination product. Overall, the structural similarities between AZD5156 and EVUSHELD suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of EVUSHELD; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 and AZD3152 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs.

The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156/AZD3152 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. This is not expected with AZD5156 or AZD3152 because, similar to EVUSHELD, they have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the EVUSHELD program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the EVUSHELD arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other EVUSHELD clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between EVUSHELD and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 and AZD3152 studies.

### 2.3.2 Benefit Assessment

AZD5156 and AZD3152 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline as shown in the Phase III PROVENT trial (Levin et al 2022). It should be noted that the comparator EVUSHELD, as well as AZD3152 and AZD5156, may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not

suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD3152 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Overall, it is considered that the AZD5156 and AZD3152 nonclinical data available to date, and clinical data from similar mAbs, including EVUSHELD, provide confidence that the overall benefit-risk is favorable.

Detailed information about the known and expected benefits and potential risks of AZD5156/AZD3152 and EVUSHELD is provided in the respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through approximately 90 days after IMP administration.<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA to AZD5156, AZD3152, and AZD1061, ADA titers |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and EVUSHELD and/or placebo | Occurrence of AEs collected through approximately 90 days after each IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus EVUSHELD and/or placebo) using a hazard regression model. |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and EVUSHELD and/or placebo administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers |
| **Exploratory** | |
| To assess the PK of AZD5156, AZD3152, and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD3152 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD3152 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits<br>Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered EVUSHELD and AZD3152 | Other exploratory assays for humoral, mucosal, and cellular immune responses, including additional SARS-CoV-2 nAb, may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| To characterize the predicted serum nAb responses to SARS-CoV-2 variants following IMP administration | Descriptive statistics for predicted GMTs will include the number of participants, geometric mean, gSD, 95% CI, summarized by treatment arm and visit for select SARS-CoV-2 variants using PK and in-vitro $IC_{50}$ values [a] |

[a] $IC_{50}$ values from prior in-vitro analysis of AZD3152 and AZD7442 in research grade pseudovirus neutralization assays will be used.

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; $IC_{50}$ = concentration giving half-maximal inhibition; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study that will be conducted in approximately 3706 participants (approximately 3256 in the Parent study and 450 in the sub-study) to evaluate the safety, efficacy, PK, and neutralizing activity of AZD3152 compared with EVUSHELD or placebo for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. The study will be conducted globally. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum. The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and AZD7442.

The Parent study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with placebo.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of

AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the sentinel cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable (for more details on the safety review, see Section 4.1.1). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Prior to CSP v7.0, the comparator for the Main Cohort was EVUSHELD as the immunobridging portion of the study was incorporated into the Parent study. At the request of regulatory authorities, a sub-study specifically for immunobridging is being undertaken (which will be conducted in the US only). As a result, the Parent study will become an efficacy and safety study, and the comparator will therefore be changed to placebo. As the comparator is given on two occasions, this means that a participant randomized to the comparator arm may receive (a) two doses of EVUSHELD, (b) a dose of EVUSHELD and a dose of placebo, or (c) two doses of placebo.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (ie, active treatment or comparator) 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and EVUSHELD use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. For the Main Cohort, AEs that occur outside of these windows between each administration that are either related to IMP, or are COVID-19 related but do not prompt an Illness Visit (eg, asymptomatic COVID-19), will be reported on the AE CRF page. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (adapted from the WHO COVID-19 case definition WHO 2022) and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants in the Sentinel Safety and Main Cohorts should refrain from receiving SARS-CoV-2 vaccines until after the Day 29 assessments have been completed. For participants in the Main Cohort, SARS-CoV-2 vaccines should not be given 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first approximately 56 participants in the study will comprise the Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Comparator Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants.

The ESDRs for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- Enrollment will be paused once 14 participants have been recruited in the initial cohorts (1a and 1b). Initial ESDRs will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDRs, enrollment of participants will continue to be paused until after Day 15. If the ESDRs conclude that the safety profile is acceptable, then enrollment will be permitted to continue, and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- Enrollment will be paused once more when 42 participants have been recruited into the final 2 cohorts (2a and 2b). Further ESDRs will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile. There is not expected to be any difference in safety profile between AZD3152 administered in combination with AZD1061 (as AZD5156) or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The safety data collected will be entered into eCRFs and reviewed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDRs:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152).

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (ie, active treatment or comparator) 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Comparator Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD3152 300 (1600) | Placebo (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Section 4.1.1.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous EVUSHELD Phase I study in pre-exposure prophylaxis (D8850C00001) and the EVUSHELD Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and efficacy.

A separate dose exploration study (D7000C00004) will be conducted to evaluate the safety and pharmacokinetics of AZD3152.

Participants in the Main Cohort will be randomized to AZD3152 (instead of the originally planned AZD5156) or placebo. The initial development plan for AZD5156 focused on a combination of two mAbs (cilgavimab [AZD1061] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered EVUSHELD by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering EVUSHELD in the gluteal region in a clinic setting and in obese individuals. Thus, off-label use of EVUSHELD administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration.

Main Cohort participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the EVUSHELD Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the main target population using EVUSHELD) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2

vaccination and thus remain at higher risk of severe COVID-19. The inclusion criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for EVUSHELD, which includes the adolescent population despite not being included in the pivotal Phase III studies. Given the expected safety and PK profile of AZD3152, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD3152 clinical development plan. The adolescent population was approved for EVUSHELD based on PK extrapolation.

### 4.2.3 Rationale for Use of Placebo as Comparator for the Main Cohort

When the study was initially designed, based on the known efficacy of EVUSHELD at that time, AstraZeneca considered EVUSHELD a more appropriate comparator for the Main Cohort than placebo. However, as the Parent study is now primarily an efficacy and safety study, as of CSP v7.0 the comparator for the Main Cohort will be placebo to facilitate feasibility and in compliance with regulatory advice.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in the Sentinel Safety Cohort of this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for EVUSHELD. Similar PK for AZD5156 and EVUSHELD have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as EVUSHELD, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD3152 Dose

The AZD5156 600 mg dose comprises AZD3152 300 mg and AZD1061 300 mg; therefore, AZD3152 300 mg will be used as the dose in the study (see Section 4.3.1). A 300 mg dose of AZD3152 is predicted to maintain nasal lining fluid concentrations of AZD3152 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.3 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals in the Sentinel Safety Cohort at low risk of development of severe COVID-19 in order to provide a blinded comparison and to allow objective assessment of the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the EVUSHELD Phase I study (D8850C00001).

In the Main Cohort, placebo will also be used as the comparator for AZD3152 (see Section 4.2.3).

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

The results from some laboratory samples may not become available until after the study completion date.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
   – Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

– Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

– The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

– All female participants of childbearing potential must have a negative urine pregnancy test result at screening.

– Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN at screening.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test prior to dosing at Visit 1.

4 Weight ≥ 40 kg at screening.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have solid tumor cancer and be on active immunosuppressive treatment
- Have hematologic malignancy
- Transplant participants must satisfy at least one of the following:
  - Have had a solid organ transplant within 2 years and / or
  - Had a hematopoietic stem cell transplant within 2 years and / or
  - Who have chronic graft-versus-host disease
  - Participants who previously had a solid organ transplant or hematopoietic stem cell transplant more than 2 years prior to Visit 1 may also be eligible based on the inclusion criterion for immunosuppressive treatment
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive biologic agents (eg, for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary (eg, DiGeorge syndrome) or secondary (eg, hemodialysis) immunodeficiency
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts < 200/$mm^3$ within 6 months of Visit 1, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)

See Appendix F for the list of qualifying immunosuppressive medications.

6 Medically stable defined as disease not requiring significant change in maintenance therapy or hospitalization for worsening disease or any recent cardiovascular event (eg, acute myocardial infarction, thromboembolic event) during the 1 month prior to

enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

- All female participants of childbearing potential must have a negative urine or serum (β-hCG) pregnancy test result at screening and Visit 1 before the administration of study intervention.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of IV or SC immunoglobulin within 6 months prior to Visit 1 or expected to receive IV and SC immunoglobulin 6 months after dosing.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study (except where the participant ceased IMP treatment >90 days and is in the follow-up period of the study and not expected to receive further IMP).

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

### 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5

Prior to receipt of the second dose of study intervention at Visit 5, participants should:

1 Have a negative rapid antigen test* for SARS-CoV-2.

2 Have a body weight ≥ 40 kg.

3 Have a negative serum or urine pregnancy test for WOCBP.

4 Not have received IV or SC immunoglobulin within 6 months prior to the second dose at Visit 5 or are expected to receive IV and SC immunoglobulin 6 months after dosing.

5 Not have received a COVID-19 vaccine within 14 days prior to the second dose at Visit 5.

6 Not have received COVID-19 antiviral for prophylaxis within 2 weeks prior to the second dose at Visit 5.

*If a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3).

Participants can wait up to 14 days to comply with criteria #5 or #6 above so as to be eligible for the second dose.

For instructions for participants who are not eligible for the second dose (Visit 5), see Section 7.1.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet

the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure or unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study, which can occur at any time during the enrollment period. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD3152 or placebo (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials.

AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD3152 in the Main Cohort, label-claim volume per vial is 2 mL.

AZD5156 (gluteal or thigh) is administered as 2 sequential IM injections, one injection for each component mAb, with the second injection administered in the contralateral side. AZD3152 will be administered as single IM injection (in the thigh). For AZD5156, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM

injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152.

Placebo will be supplied locally by the site. In the Sentinel Safety Cohort placebo will be administered as 2 IM injections, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). In the Main Cohort, placebo will be administered as a single IM injection in the thigh.

**Table 8 Investigational Medicinal Products**

| Intervention name | AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort [a] | AZD3152 for Main Cohort [a] | Placebo (Comparator) for Sentinel Safety and Main Cohorts |
|---|---|---|---|
| **Type** | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD3152 will be supplied as a single vial.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 300 mg AZD3152 at 150 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 300 mg single dose of AZD3152 | Single dose |
| **Vials required for constitution** | AZD1061; 2 vials<br>AZD3152; 1 vial | 1 vial | NA |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** [a] | **AZD3152 for Main Cohort** [a] | **Placebo (Comparator) for Sentinel Safety and Main Cohorts** |
|---|---|---|---|
| **Route of administration** [b] | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 1 IM injection (thigh) of 2 mL of AZD3152 | Sentinel Safety Cohort: 2 IM injections (gluteal or thigh); 3 mL and 2 mL<br>Main Cohort: 1 IM injection (thigh): 2 mL |
| **Use** | Investigational | Investigational | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

[b] The second injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The Investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156, AZD3152, and placebo for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (ie, the individual

storage time limits are not additive). AZD5156, AZD3152, and placebo do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD3152 or placebo (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and EVUSHELD use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD3152, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system

- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples (including the AstraZeneca Bioanalytical monitor).
- The unblinded Biometric teams (Statisticians and Programmers) both at AstraZeneca and its delegate and the DSMB.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy. SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5.1.2). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. All routine vaccines are permitted; however, they should not be given within 14 days before or after Visit 1 dosing of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 14 days before Visit 1 or during the study until at least after Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. The use of vitamins or occasional use of over-the-counter medications (eg, paracetamol, ibuprofen, antihistamines) would not exclude an individual from enrolling in the study.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | All routine vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments, and subsequently should not be given from 14 days prior to the second dose at Visit 5 until after the Day 210 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks prior each dose (Visit 1 or Visit 5) as well as during the study until after the Day 29 assessments following the first dose, and after the Day 210 assessments following the second dose of study intervention. If the participant develops COVID-19, standard of care treatment is allowed. |
| | Immunoglobulins (IVIG or SCIG) | Receipt of IV or SC immunoglobulin within 6 months prior to Visit 1 or expected to receive IV and SC immunoglobulin 6 months after each dose. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to the first dose of IMP and until 6 months after the last dose of IMP. |

IMP = investigational medicinal product; IVIG = intravenous immunoglobulins; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCIG = subcutaneous immunoglobulins.

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD3152 or placebo), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose.

If the participant experiences an immediate hypersensitivity reaction after their first dose of study intervention, the participant will be excluded from receiving a second dose of study intervention at Visit 5. If this occurs, the participant should remain in the study to be evaluated and complete all the remaining assessments as indicated in the SoA (Section 1.3). Also, if the participant is not eligible for the second dose (Visit 5), the participant should remain in the study to be evaluated and complete all the remaining assessments as indicated in the SoA. In the opinion of the Investigator or Sponsor, if any significant events should occur, this should be assessed and decided by the Investigator as to whether the participant should proceed in the study or be discontinued.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156. AstraZeneca will make the final decision after analysis of the safety data.

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any Grade 3 or higher AEs in 2 or more participants, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Main Cohort

The study will be put on temporary hold (defined as a pause in enrollment and/or dosing of participants into the Main Cohort) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In the event of a temporary hold for safety reasons, AstraZeneca will carefully review the totality of data and the risk to all participants will be evaluated thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing. If AstraZeneca determines that the study may be resumed, this may occur without a protocol amendment.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that, in the opinion of the Sponsor, may preclude further administration of IMP.
- If one or more participant experiences a grade IV hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If two or more participants, within the first 300 participants, experience a grade III or higher hypersensitivity reaction.
- If two or more participants, within the first 300 participants, experience a grade III or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with study intervention until the relevant safety review has been conducted.

If the study is suspended or the decision is made not to proceed to the Main Cohort, a protocol amendment will be submitted to Health Authorities.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 variants (Alpha, Omicron BA.2, Omicron BA.4/5, and Omicron XBB.1.5), using validated pseudovirus neutralization assays. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152.

### 8.1.2 Participant-reported COVID-19 Symptoms

For participants in the Main Cohort, to determine the incidence of infection, study sites will contact all participants weekly (prior to Day 361) and then monthly (from Day 361) (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (adapted from the WHO COVID-19 case definition WHO 2022) from the past week. An Unscheduled Visit should be conducted if a participant reports any COVID-19-like symptoms. At the Unscheduled Visit, the Investigator should discuss all symptoms the participant is experiencing including those that are mild to determine if the participant meets the clinical criteria adapted from the WHO COVID-19 case definition for an Illness Visit. If the participant meets the case definition, the COVID-19 initial assessment is started.

The Investigator site will need to conduct Illness Visits within 3 days of the qualifying symptoms being reported (see Section 8.1.3 for more on Illness Visits). Participants who develop any symptoms that could be due to COVID-19 must be advised to contact the study site as soon as possible.

Illness Visits should only be initiated if a participant meets either of the following criteria adapted from the WHO COVID-19 case definition clinical criteria (WHO 2022):

- Any two of the following: fever*, cough, positive COVID-19 test (rapid antigen test or RT-PCR)

OR

- Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever*, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia, conjunctivitis, positive COVID-19 test, symptom as judged by the Investigator to be related to COVID-19

*Subjective definition to be used for fever.

Participants who present with COVID-19 qualifying symptoms after Visit 1 in the Main Cohort will be instructed to attend the study site for Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever [≥ 38°C], cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020.

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site illness visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is

available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

At IL-D1, the study site will set up an illness e-Diary on the participant's own cellphone or equivalent device. If a participant does not have a suitable device the study site will issue an Illness e-Diary device. The study site will train the participant on how and when to complete the e-Diary and document their daily symptoms. Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in the Illness e-Diary. The status of ongoing symptoms reported in the e-Diary at the end of an illness series will be recorded. The end date for any symptoms still present after 14 days will be documented in the eCRF. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

For the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants are to be encouraged to contact the site if their symptoms worsen.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Visit 5 (administration of the second dose of IMP) is only allowed to overlap with IL-D14. If Visit 5 is scheduled to occur at any of the other Illness Visit days, it should be delayed to IL-D14.

The Illness Visit assessment pathway may be initiated more than once (up to 10 times) for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories.

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of SARS-CoV-2 Spike protein mutations identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs, and any observations will be documented in the participant's medical records (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding from the time of study intervention administration should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again 10 to 15 minutes after the second injection is given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Electrocardiograms

A single 12-lead ECGs will be performed at screening for the Sentinel Safety Cohort and Main Cohort (time points specified in the SoA; see Section 1.3). A 12-lead ECG will be obtained after 5 minutes' supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal, borderline, or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as unscheduled assessments.

All ECG readings will be digitally stored as source documents.

### 8.2.4 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort (see Section 1.3.1, Section 1.3.2, and Section 1.3.3).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea (or blood urea nitrogen) | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T oI (Main Cohort; screening only) |
| Glucose (random) | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) (or international normalized ratio) |
| **Other (women of childbearing potential only)** | |
| Urine serum (β-hCG) pregnancy test | Follicle stimulating hormone [a] |

[a] For female participants aged < 50 years who are considered postmenopausal, will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.

β-hCG = beta human chorionic gonadotropin; ULN = upper limit of normal.

For female participants aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine or serum pregnancy test will be performed locally at screening (both cohorts), Visit 1 (both cohorts), and Visit 5 (Main Cohort only). For Visits 1 and 5, urine pregnancy test must be performed and be negative prior to dosing. This is especially important for any female participants who have not reached menarche at enrollment into the study and

whose child-bearing potential is expected to change during the study. A serum pregnancy test may be performed if a urine pregnancy test is not possible.

### 8.2.5 Other Safety Assessments

#### 8.2.5.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.5.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling may be recorded in the medical record at site visits.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after, 30 minutes (+ 10 minutes), and 1 hour after both injections are complete and also prior to participant release. Injection site reactions will also be monitored on Visit 2 (Day 3), Visit 3 (Day 5) and Visit 4 (Day 8) for the Sentinel Safety Cohort and Visit 2a (Day 8) and Visit 6 (Day 189) for the Main Cohort.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording

events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following each administration of study intervention. Adverse events occurring after 90 days following each study intervention administration and assessed by the Investigator as having a causal relationship to IMP and/or is COVID-19-related but does not prompt an Illness Visit (eg, asymptomatic COVID-19) will be collected in the eCRF. Serious adverse events, MAAEs, and AESIs will be collected throughout the study.

Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156, AZD3152, and EVUSHELD in this study are based on those identified for EVUSHELD and are as follows:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoAs (Section 1.3).

Medically attended adverse events are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits (including Illness Visits themselves) will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE

within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156/AZD3152 and the active comparator product EVUSHELD are the respective Investigator's Brochures for the individual products.

### 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.10.1 Maternal Exposure

The IMP should not be given to pregnant women.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD3152, AZD5156, and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD3152 and (prior to CSP v7.0) AZD7442 from the Main Cohort, AZD5156 from the Sentinel Safety Cohort, and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156, AZD3152, and (prior to CSP v7.0) AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, serum samples will be collected and analyzed for the first 1200 participants (approximately). Serum samples will be collected for the rest of the participants for potential analysis as needed. Nasal lining fluid PK samples will be collected only for the first 600 participants (approximately). Samples from participants who receive placebo will be analyzed if required. Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$;

- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD1061, AZD3152, and AZD8895 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated bioanalytical methods. For the Main Cohort, samples will be collected and analyzed for the first 1200 participants (approximately). Serum samples will be collected for the rest of the participants for potential analysis as needed. Samples from participants who receive placebo will be analyzed if required. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, including additional SARS-CoV-2 nAb, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD3152.

For storage, re-use and destruction of biomarker samples see Section 8.5.

#### 8.6.2.1 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing peripheral blood mononuclear cells using methods that may include flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor. Samples will be collected at Illness Visit time points specified in the SoAs (Section 1.3). Additionally, plasma may be isolated from the whole blood samples collected to isolate peripheral blood mononuclear cells, which can be utilized for exploratory immunogenicity and biomarker analyses.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants randomized to the comparator arm in the Main Cohort may have received doses of EVUSHELD or placebo at either first or second IMP administration and will be presented as a combined comparator study arm for the efficacy evaluation. Safety data will be summarized by each comparator group (EVUSHELD or placebo) separately and combined. When appropriate, actual dose(s) received may be presented separately to the combined comparator group. Any participant who received or was assigned to EVUSHELD at the first or second IMP dose will be presented as having received or been assigned to EVUSHELD. The SAP will provide details on the presentation of data by assigned and actual treatments received.

## 9.1 Statistical Hypotheses

The primary efficacy objective is to compare participants dosed with AZD3152 to participants dosed with EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 observed up to 181 days after the participant's last dose. A superiority test will be performed to compare the hazard rate of symptomatic COVID-19 between treatment arms. The null hypothesis will be rejected if the HR 95% CI upper bound is less than 1.0 using a 2-sided test at a significance level of 5% ($\alpha = 0.05$). If the null hypothesis is rejected in favor of the alternative hypothesis, it will be concluded that the data provide evidence AZD3152 is superior to comparator in preventing symptomatic COVID-19 during the study period. The

hypotheses are as follows:

$$H_0: \quad \frac{\lambda_{\text{AZD3152}}}{\lambda_{\text{comparator}}} \geq 1.0,$$

$$H_A: \quad \frac{\lambda_{\text{AZD3152}}}{\lambda_{\text{comparator}}} < 1.0,$$

where $\lambda_{\text{AZD3152}}$ and $\lambda_{\text{comparator}}$ are the instantaneous symptomatic COVID-19 hazard rate of AZD3152 and comparator arms, respectively.

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the Parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD3152 or comparator.

The overall symptomatic COVID-19 blinded event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed.

The sample size in the Main Cohort is driven by the total number of events required to demonstrate the efficacy of AZD3152 versus comparator in the prevention of symptomatic COVID-19. A target sample of approximately 3200 participants has been selected to reach the required number of events. Approximately 40 events will provide at least 90% power to demonstrate that the lower bound of the 2-sided 95% CI is less than 1, under the assumption that the annual event rate will be approximately 3.2% in the comparator arm, HR of 0.30 (70% efficacy), significance level of $\alpha = 0.05$, and 10% attrition. Assumptions are based on data from prior studies with EVUSHELD and reported estimates of the event rate among those with immunocompromising conditions (Kelly et al 2022).

The Main Cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD3152 compared with 1600 participants receiving comparator within the study.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | These populations will consist of all randomized participants who received part or all of study intervention. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. Participants in the FAS will be classified according to the assigned treatment. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Anti-drug antibody analysis set | All safety analysis set participants with a non-missing baseline and at least one non-missing post-baseline ADA result of the mAb component(s) evaluated. EVUSHELD and AZD5156 participants will be considered ADA-evaluable if either one or both of the respective mAb components includes a baseline and post-baseline result of the individual component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the indicated treatment classification in the corresponding analysis set population.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses. Methods for controlling multiplicity across endpoints will be presented in the Statistical Analysis Plan.

### 9.4.2 Efficacy

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops their first symptoms for COVID-19 at any time up to Visit 9 (Day 361). Positive cases require a central RT-PCR test and meet the qualifying symptoms as indicated by the Investigator satisfying the modified WHO definition of symptomatic COVID-19 (see Section 8.1.2). Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to compare prophylactic efficacy (ie, 1-HR) of AZD3152 versus comparator. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Participants who become unblinded to treatment assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding or receipt of the first dose of COVID-19 preventive product. Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and will be included in the analysis. Participants who withdraw early from the study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

Other efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through

Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis of secondary efficacy endpoints.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by SARS-CoV-2 variant, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers with SARS-CoV-2 variants, including Alpha, Omicron BA.2, Omicron BA.4/5 and Omicron XBB.1.5 between treatment groups will be conducted using GMT ratio. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152. Analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

### 9.4.4 Anti-drug Antibody Variables

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed. Further details are provided in the SAP.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, where possible, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of the 2 component mAbs of AZD5156. The following single dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or EVUSHELD, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

## 9.5 Planned Analyses

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK concentrations at Day 29. The remaining two analyses will include all available data when conducted.

The study will maintain a double-blind period until a median follow-up time is greater than 181 days in the Full analysis set (FAS) and approximately 40 or more participants have confirmed symptomatic COVID-19 to support the primary efficacy and safety objectives and trigger the primary analysis. To maintain the integrity of the study for rigorous evaluation of safety and efficacy through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analyses will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan. Participant-level unblinding information will be kept strictly confidential, and the rationale for any unblinding will be documented. An additional interim analysis may be conducted to evaluate efficacy of the first IMP dose through day 181, safety and PK of the second dose at Visit 7 (Day 210). This analysis will only be conducted if the primary analysis has been previously conducted and all participants have been followed for more than 181 days or withdrawn from the study. The SAP will describe the planned analyses in greater detail.

If there is a medical need for AZD3152 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis and data readouts that may reveal treatment assignments if conducted prior to the primary analysis.

## 9.6 Safety Review Committee – Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort, as discussed in Section 4.1.1.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but

are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
   (a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   (a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   (b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 13, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care.

# Appendix F List of Immunosuppressive Medications

The list of immunosuppressive medications in the table below is not exhaustive.

| **1. Alkylating Agents** | | | |
|---|---|---|---|
| Bendamustine | | Melphalan | |
| Busulfan | | Mitomycin | |
| Carboplatin | | Oxaliplatin | |
| Carmustine | | Procarbazine | |
| Cisplatin | | Streptozocin | |
| Cyclophosphamide | | Temozolomide | |
| Dacarbazine | | Thiotepa | |
| Ifosfamide | | Trabectedin | |
| Lomustine | | | |
| **2. Selective Immunosuppressants** | | | |
| General | | Calcineurin Inhibitors | Antimetabolites |
| Azathioprine | Lenalidomide | Cyclosporine | Methotrexate |
| Belumosudil | Mycophenolate | Tacrolimus | Nelarabine |
| Bortezomib | Pomalidomide | Voclosporin | Pemetrexed |
| Cladribine | Teriflunomide | | Pralatrexate |
| Dimethyl fumarate | Thalidomide | | Irinotecan |
| Diroximal fumarate | Anti-thymocyte immunoglobulin (horse, rabbit) | | Liposome |
| Leflunomide | | | Capecitabine |
| | | | Clofarabine |
| | | | Cytarabine |
| | | | Decitabine |
| | | | Floxuridine |
| | | | Fludarabine |
| | | | Fluorouracil |
| | | | Gemcitabine |
| | | | Mercaptopurine |
| JAK Inhibitors | | mTOR Inhibitors | Sphingosine-1-phosphate Receptor Modulators |
| Baricitinib | | Everolimus | Fingolimod |
| Tofacitinib | | Sirolimus | Ozanimod |
| Upadacitinib | | | Ponesimod |
| Peficitinib | | | Siponimod |
| Itacitinib | | | |
| **3. Monoclonal Antibodies** | | | |
| General | | Anti-IFN | Anti-CD20 |
| Alemtuzumab (anti-CD52) | | Anifrolumab | Ibritumomab |
| Belimumab | | Emapalumab | Obinutuzumab |
| Begelomab (anti DPP-4/CD26) | | | Rituximab |
| Teprotumumab (anti-IGF-1) | | | Ocrelizumab |
| Inebilizumab (anti-CD19) | | | Ofatumumab |
| Muromonab (anti-CD3) | | | |
| Inotuzumab Ozogamicin (anti-CD22) | | | |

| Selective T-Cell Costimulation Blockers | Integrin Receptor Agonists | Bruton Tyrosine Kinase Inhibitors | |
|---|---|---|---|
| Abatacept<br>Belatacept | Natalizumab<br>Vedolizumab | Ibrutinib<br>Acalabrutinib<br>Pirtobrutinib | Zanubrutinib<br>Deucravacitinib |
| Complement Inhibitors | TNF-alpha Inhibitors | IL-23 Inhibitors | |
| Pegcetacoplan<br>Eculizumab (anti-C5)<br>Ravulizumab (anti-C5)<br>Sutimlimab (anti-C1) | Adalimumab<br>Afelimomab<br>Certolizumab Pegol<br>Etanercept<br>Golimumab<br>Infliximab | Ustekinumab<br>Guselkumab<br>Tildrakizumab<br>Risankizumab | |
| IL-17 Inhibitors | IL-1 Inhibitors | IL Inhibitors (other) | |
| Secukinumab<br>Ixekizumab<br>Bimekizumab<br>Brodalumab<br>Netakimab | Anakinra<br>Canakinumab<br>Rilonacept | Basilximab (anti IL-2)<br>Sarilumab (anti IL-6)<br>Satralizumab (anti IL-6)<br>Siltuximab (anti IL-6)<br>Tocilizumab (anti IL-6)<br>Spesolimab (anti IL-36) | |
| **4. Steroids** | | | |
| Dexamethasone: ≥ 3 mg per day, minimum of 2 weeks of therapy<br>Prednisolone: ≥ 20 mg per day, minimum of 2 weeks of therapy<br>Prednisone: ≥ 20 mg per day, minimum of 2 weeks of therapy | | | |

CD = cluster of differentiation; DPP = dipeptidyl peptidase; IFN = interferon; IFG = insulin-like growth factor; IL = interleukin; TNF = tumor necrosis factor.

# Appendix G Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 6.0 [24 May 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended primarily to add a sub-study as an Addendum to the Parent study, to upgrade efficacy to a primary endpoint, and to provide additional clarification of the study design elements that impact the recruitment of the Main Cohort.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page<br>Synopsis<br>2.1 Study Rationale<br>3 Objectives and Endpoints<br>4.1 Overall Design<br>4.2 Scientific Rationale for Study Design<br>9 Statistical Considerations | Efficacy has been upgraded to a primary endpoint<br><br>nAb responses to the SARS-CoV-2 Alpha variant is no longer a primary endpoint for the Main Cohort | To allow the collection of efficacy data to support a 300 mg dose<br><br>In accordance with regulatory guidance, the immunobridging objective will be explored through the sub-study |
| Synopsis<br>2.1 Study Rationale<br>4.1 Overall Design | Added text to introduce the inclusion of a separate SUPERNOVA sub-study as an Addendum | Based on FDA feedback, a sub-study has been added to be conducted in the US only |
| Synopsis<br>3 Objectives and Endpoints | Added AZD5156, AZD3152, and AZD1061, ADA titers to the incidence of ADA endpoint for the secondary objective of ADA response evaluation for the Sentinel Safety Cohort | For clarification. |
| Synopsis<br>3 Objectives and Endpoints<br>8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments<br>9 Statistical Considerations | Revised the secondary endpoint for the Main Cohort for the comparison of the nAb responses to the SARS-CoV-2 variants. The text has been updated to specify Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and AZD7442 administration | To add additional SARS-CoV-2 variants as the primary nAb endpoint with nAb responses to the SARS-CoV-2 Alpha variant was removed |
| Synopsis<br>3 Objectives and Endpoints<br>8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments<br>9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Added text to reflect that additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152 | Additional text was added to ensure additional SARS-CoV-2 variants will be assessed |
| Synopsis<br>3 Objectives and Endpoints | Added AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers to the incidence of ADA endpoint for the secondary objective of ADA response evaluation for the Main Cohort | For clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>4.1 Overall Design<br>4.1.1 Sentinel Safety Cohort<br>9.2 Sample Size Determination | Added "approximately" to "56 healthy adults" | To allow for any small number of additional participants in the Sentinel Safety Cohort |
| Synopsis<br>9 Statistical Considerations | Section has been updated | Changes added to align with the upgrading of efficacy to a primary endpoint and the removal of the primary endpoint of nAb responses to the SARS-CoV-2 Alpha variant |
| 1.3 Schedule of Activities<br>1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Updated the screening period for the Main Cohort participants to "up to 14 days (Day -14 through Day 1)" | To facilitate the collection of medical history information |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Removed the assessment of eligibility criteria verification from Visit 5, and added a new row to verify selected eligibility criteria for receipt of second dose (Visit 5) with footnote [c] to see Section 5.2.3 | To clarify the eligibility criteria for receipt of second dose of study intervention |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added a new footnote [d] to the full physical examination assessment during the Early Discontinuation Visit to exclude height measurement in adults aged 18 years and older during the assessment | For clarification. |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>5.2.2 Exclusion Criteria (Main Cohort)<br>8.2.4 Clinical Safety Laboratory Assessments | Updated the pregnancy testing to reflect that a serum pregnancy test may be substituted for a urine pregnancy test where a urine pregnancy testing is unavailable | This change has been made to allow for pregnancy testing in female participants who are unable to produce urine |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added a new footnote [h] to the rapid antigen test for SARS-CoV-2 (performed locally) assessment at Visit 5 to note that if a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive | To provide flexibility regarding the second dose administration of IMP in participants who have a positive rapid antigen test at Visit 5 and aligned to Section 8.1.3 on Illness Visits. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3) | |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.1.2 Participant-reported COVID-19 Symptoms | Added a new row for assessments of "Monthly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms", adjusted footnote [l] (previous footnote [i]) for clarification | Telephone contact will take place weekly prior to Day 361, and monthly from Day 361 to reduce the site and participant burden |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>4.1 Overall Design<br>8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Added footnote [m] and updated text in Sections 4.1 and 8.3.1 to clarify that AEs occurring after 90 days following each study intervention administration and assessed by the Investigator as having a causal relationship to IMP and/or COVID-19-related but does not prompt and Illness Visit (eg, asymptomatic COVID-19) will be collected on the AE CRF page | This change has been made in case events occur outside of the AE windows (after 90 days following each study intervention) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.5.1.1 Determination of Drug Concentration<br>8.5.2.1 Anti-drug Antibody Assessments | Removed footnote [o] (previous footnote [k]) from assessments of PK serum sample and ADA and antidrug nAbs assessment serum sample and accordingly updated the text in Sections 8.5.1.1 and 8.5.2.1 to clarify that nasal lining fluid PK samples will only be collected for the first 600 participants (previously 1200 participants) | To extend the analysis of PK, ADA, and antidrug nAbs to the full enrolled population<br>Reduced the number of nasal lining fluid samples to 600 as the previous number of 1200 was aligned to the immunobridging endpoint, which has now been removed from this protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added "and 1 hour" to footnote [p] | This change has been made to allow evaluation of safety and tolerability 1 hour after both injections are given and also aligned to Section 8.2.5.2 on Immediate Adverse Events which are assessed 1 hour after both injections |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added a column for the Unscheduled Visit to verify qualifying symptoms with footnote [d] to clarify that if the participant meets the clinical criteria adapted from WHO COVID-19 case definition, then an illness visit (IL-D1) will be initiated | Added a column to clarify the requirements for the Unscheduled Visit and for which an Illness Visit series should be initiated |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Updated the window for Visit IL-D14 to + 2 days | The participant e-Diary will need to be completed up to and including IL-D14 |
| | Updated footnote [e] to reflect that central RT-PCR laboratory test results may not be reported to sites during the Illness Visit period | For clarification |
| | Telephone contact for safety monitoring has been added to the visits IL-D5 and IL-D11 and footnote [f] has been added to note that for the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen | This change has been added to ensure telephone contact is made with the participant on each home Illness Visit |
| | Added “WHO Clinical Progression Scale” assessments to the Illness Visits with footnote [f] for clarification | To clarify that the WHO Clinical Progression Scale score is required for each site Illness Visit |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Changed “Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic” to “Coronavirus SARS-CoV-2 is the causative agent of COVID-19” | Updated to the current WHO status for COVID-19 |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Changed “against the more recent Omicron variants BA.2, BA.3, and BA.4/5” to “against some of the | To add clarity since additional variants have emerged |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | more recent Omicron variants such as BA.2, BA.3, and BA.4/5" | |
| 3 Objectives and Endpoints | Added an exploratory objective to characterize the predicted serum nAb responses to SARS-CoV-2 variants following IMP administration. The endpoint will be descriptive statistics for predicted GMTs will include the number of participants, geometric mean, gSD, 95% CI, summarized by treatment arm and visit for select SARS CoV-2 variants using PK and in-vitro $IC_{50}$ values | To align with the removal of the primary immunobridging endpoint, this exploratory objective has been added to characterise nAb titers associated with each treatment arm |
| 4.1 Overall Design<br>6.5 Concomitant Therapy | Updated text to reflect that SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments, and subsequently should not be given from 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments | The timing of the restriction was re-aligned from Day 29 to the assessments that occur at Visit 3 which may occur up to 3 days post Day 29, as per the 3-day visit window. Restrictions of SARS-CoV-2 vaccines added to the second dose, were included to prevent confusion around possible reactogenicity of the vaccine at the time of the second dose being administered |
| 4.1 Overall Design<br>8.1.2 Participant-reported COVID-19 Symptoms | Updated text to reflect that the clinical criteria for SARS-CoV-2 infection in the protocol is adapted from the WHO COVID-19 case definition and a reference to the most recent WHO COVID-19 case definition (July 2022) has been added | Clinical criteria for SARS CoV-2 infection in this protocol have been adapted from the WHO COVID-19 case definition |
| 5.2.1 Inclusion Criteria (Main Cohort) | Updated Inclusion criterion #3 to reflect that participants should have a negative rapid antigen test prior to dosing at Visit 1 and removed "Visit 5" | This change has been made to note that a negative rapid antigen test must be obtained prior to the first dose of study intervention to confirm eligibility for entry into the study. Visit 5 was removed from the entry criteria given that the participant is already entered into the study, and instead eligibility for the second dose of study intervention will be verified at Visit 5 |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Updated Inclusion criterion #4 to reflect that participants weights should be ≥ 40 kg at screening and removed "Visit 5" | To ensure that the participant has a safe weight for receiving study intervention to confirm eligibility for entry into the study. Visit 5 was removed from the entry criteria given that the participant is already entered into the study, and instead eligibility for the second dose of study intervention will be verified at Visit 5 |
| | For Inclusion criterion #5, changed "active treatment" to "active immunosuppressive treatment" (first bullet), and removed the examples | To clarify the active treatment must be immunosuppressive. The examples were excluded as they would not meet the new definition |
| | Updated the inclusion criteria of participants who previously had a transplant (third bullet) | To clarify the inclusion of participants who previously had a transplant |
| | Changed "other immunosuppressive or immunomodulatory biologic agents" to "other immunosuppressive biologic agents" (fourth bullet) | To ensure that the entry criteria include those participants who are on medication that leave them immunosuppressed |
| | Removed "Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia" (seventh bullet) | Text removed to be consistent with Exclusion criterion #8 regarding the use of IVIG and SCIG |
| | For Inclusion criterion #6, changed "change in therapy" to "change in maintenance therapy" and added "or any recent cardiovascular event (eg, acute myocardial infarction, thromboembolic event)" | Added language around therapy for clarification, and additional language including cardiovascular events to ensure participant is medically stable prior to study entry |
| 5.2.2 Exclusion Criteria (Main Cohort) | Updated Exclusion criterion #1 to include a negative serum pregnancy and that a negative urine or serum pregnancy test must be obtained prior to Visit 1 | This change was made because a urine pregnancy test is not possible in all female participants and to note that a negative pregnancy test should be obtained prior to both the first and second dose of study intervention |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Added Exclusion criterion #8, to state that participants being treated with intravenous or subcutaneous immunoglobulins (IVIG or SCIG) within 6 months prior to Visit 1 or are expected to receive IVIG or SCIG within 6 months after dosing should be excluded from the study | IVIG/SCIG treatment may confound the neutralizing antibody results |
| 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5 | New section | This section has been added to clarify the eligibility criteria prior to receipt of the second dose of study intervention at Visit 5 |
| 5.4 Screen Failures | Updated the text to remove the 2-week window in which the single rescreening could occur and added text to specify that the rescreening can occur at any time during the enrollment period | Removed the 2-week window to reflect the immunocompromised population |
| 6.1 Study Intervention(s) Administered | Updated Table 8 to indicate how many vials are required to constitute AZD1061, AZ8895, and AZ3152 | For clarification |
| 6.5 Concomitant Therapy | Updated Table 9 to reflect that participants must not have COVID-19 antivirals for prophylaxis 2 weeks prior to Visit 1, and during the study until after the Day 29 assessments following the first dose, and after the Day 210 assessments following the second dose of study intervention | This change was made to note that the restrictions for COVID-19 antivirals applies to both the first and second dose of study intervention, so as to avoid confounding the results of the immune sampling. The timing of the restriction was re-aligned from Day 29 and Day 210 to the assessments that occur at Visit 3 and Visit 7 which may occur up to 3 days post Day 29 and Day 210 respectively, as per the 3-day visit window |
| | Updated Table 9 to include intravenous or subcutaneous immunoglobulins (IVIG or SCIG) in “restricted” | IVIG/SCIG treatment may confound the study results and therefore, has been excluded from the study |
| | Updated Table 9 to reflect EVUSHELD should not be given within 6 months prior to each dose of IMP and until 6 months after the last dose of IMP | EVUSHELD treatment may confound the study results and therefore the criteria around the timing have been clarified |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.1 Discontinuation of Study Intervention | Updated the text to reflect that if the participant experiences an immediate hypersensitivity reaction after either IM injection, the participant will be excluded from receiving a second dose of study intervention at Visit 5 and that the participant will continue in the study and complete all scheduled assessments and sampling to end of the study | Clarification around receiving the second dose following hypersensitivity reactions |
| | Updated the text to reflect that participants who miss or are not eligible to receive the second dose of study intervention will continue in the study and complete all scheduled assessments and sampling to end of the study | For clarification |
| 7.2.2 Stopping Rules for Main Cohort | New section | Section 7.2.2 has been added to specify stopping rules for the Main Cohort |
| 8.1.2 Participant-reported COVID-19 Symptoms | Updated text to clarify the participants for which an Unscheduled Visit should be conducted and for which an Illness Visit series should be initiated | Clarified the participants for which an Unscheduled Visit should be conducted and for which an Illness Visit series should be initiated |
| | Updated the clinical criteria for SARS-CoV-2 infection based on those adapted from the WHO COVID-19 case definition | Clinical criteria for SARS-CoV-2 infection in this protocol have been adapted from the WHO COVID-19 case definition to account for a positive COVID-19 test performed off-site and any potential new symptoms that could develop given the rapidly changing landscape of COVID-19 variants |
| | Clarified that fever is subjective for the clinical criteria adapted from WHO COVID-19 case definition | Updated to clarify that a subjective assessment of fever will be utilized |
| | Added text to define fever for severe COVID -19 at ≥ 38°C. | For clarification. |
| 8.1.3 Illness Visits | Text added to reflect that the study site will set up an illness e-Diary on the participant's own device (if available) as the primary approach | For clarification. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Text added to reflect that for the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen | Clarification provided to ensure study sites follow-up with the participants for symptoms and safety information |
| | Text added to state that Visit 5 (administration of the second dose of IMP) is only allowed to overlap with IL-D14. If Visit 5 is scheduled to occur at any of the other Illness Visit days, it should be delayed to IL-D14. | To prevent IMP dosing during an Illness Visit assessment pathway. |
| 8.2.3 Electrocardiograms | Added text to clarify that a single 12-lead ECG will be performed at screening for the Sentinel Safety Cohort and Main Cohort | For clarification |
| | Changed “normal or abnormal” to “normal, borderline, or abnormal” | For clarification |
| 8.2.5.2 Injection Site Reactions | Added text to state that injection site monitoring will also be performed at 1 hour after both injections for the study intervention dose are given, and that injection site reactions will be monitored on on Visit 2 (Day 3), Visit 3 (Day 5) and Visit 4 (Day 8) for the Sentinel Study and Visit 2a (Day 8) and Visit 6 (Day 189) for the Main Study | This change has been made to align with Section 8.2.5.2 on Immediate Adverse Events which are assessed 1 hour after both injections |
| 8.3.2 Follow-up of AEs and SAEs | Removed “maximum severity grade” from adverse event variables | Maximum severity grade will be derived and therefore is not required to be collected from the CRF |
| 8.3.5 Medically Attended Adverse Events | Added text to clarify that Illness Visits themselves will not be considered as MAAEs | Clinic visits for scheduled procedures are not considered MAAEs |
| 8.3.10.1 Maternal Exposure | Added text to state that the IMP should not be given to pregnant women | For clarification of safety requirements |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.5.2.1 Anti-drug Antibody Assessments | Updated ADA to AZD1061, AZD3152, and AZD8895 will be determined (removed AZD5156 and AZD7442) | To clarify individual monoclonal antibodies to be evaluated. |
| Appendix F List of Immunosuppressive Medications | Added a new Appendix | To clarify which medications taken by participants will qualify them as immunocompromised |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms<br>4.1 Overall Design<br>8.1.3 Illness Visits | Updated text to clarify that duplicate sampling is not required where Main and Illness Visits overlap and added a reference to the Laboratory Manual | For clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | Changed “some markets” to “some regions”<br>Changed “at least some protection against SARS-CoV-2” to “at least some potential protection against SARS-CoV-2” | For clarification |
| 6.5 Concomitant Therapy | Changed “All other vaccines” to “All routine vaccines” | For consistency with Table 9 |
| 8.1.3 Illness Visits | Changed “site visits” to “site illness visits”<br>Added “up to 10 times” for Illness Visit initiations | For clarification<br>For clarification |
| 8.2.2 Vital Signs | Changed “after both injections” to “after the second injection” | This change has been made to clarify that vital signs will be monitored at 10 to 15 minutes after the second injection of the dose of study intervention is given |
| 8.2.3 Electrocardiograms | Added text to clarify that a single 12-lead ECG will be performed at screening for the Sentinel Safety Cohort and Main Cohort | For clarification |

**CSP Version 5.0 [07 February 2023]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| TITLE PAGE | The study intervention has been changed from 'AZD5156' to 'AZD5156/AZD3152' and a similar change has been made to the study title | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy, although AZD5156 will still be studied in the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of follicle stimulating hormone at screening | Required for eligibility criteria |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples have been removed from Day 271 and the EDV | Rationalization of blood sampling to reduce invasive procedures |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 2.1 Study Rationale | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.3 Benefit/Risk Assessment | Section updated throughout to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and overall benefit/risk conclusion aligned with Investigator's Brochure. | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy; also text aligned with Investigator's Brochure |
| 3 OBJECTIVES AND ENDPOINTS | Created separate primary and secondary objectives and endpoints for the Sentinel Safety and Main Cohorts | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.1 Overall Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.2 Main Cohort | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2 Scientific Rationale for Study Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | New section | Justification as to why AZD7442 is considered a better choice of control than placebo |
| 4.3.2 Justification for AZD3152 Dose | New section | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #10, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #21, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, any alkylating agents will qualify as a risk factor, not just high-dose agents | Low-dose cyclophosphamide is used as immunotherapy in lymphoma, breast and ovarian cancer |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, a moderate or severe secondary immunodeficiency will now qualify as a risk factor | To broaden the study population |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #11, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #13, noted that concurrent participation in another interventional study where the participant ceased IMP treatment >90 days who is in the follow-up period of the study and not expected to receive further IMP is permitted for inclusion | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #17, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.1 Study Intervention(s) Administered | The whole section (including the table) has been updated to reflect the use of AZD3152 as a standalone therapy in the Main Cohort, including use of placebo to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.5 Concomitant Therapy | Added more details regarding permitted concomitant medications for the Sentinel Safety Cohort and clarified the wording around SARS-CoV-2 vaccines and COVID-19 antivirals | Clarification |
| 8.5.1.1 Determination of Drug Concentration | Serum PK samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 8.5.2.1 Anti-drug Antibody Assessments | Samples for determination of ADA will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 9.1 Statistical Hypotheses | The whole section has been updated to reflect the use of AZD3152 as a standalone therapy | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.2 Sample Size Determination | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156; minor adjustments made to wording of sample size determination | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Schema updated in line with applicable changes from the protocol text | Schema made consistent with amended text |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Timing of Day 1 urine pregnancy test changed from 'prior to randomization' to 'predose' and footnote updated to clarify test must be on same day as dosing | Consistency with other parts of the table |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Clarified that laboratory safety samples on Day 1 will be taken predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Noted that duration of recording daily symptoms associated with COVID-19 will be 14 days | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 4.1 Overall Design | Wording regarding qualification for Illness Visits has been updated | Clarification |
| 4.1.1 Sentinel Safety Cohort | Added justification for use of AZD5156 safety data to initiate dosing with AZD3152 in the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.1 Rationale for Administration Site | Removed reference to components of the study interventions being monoclonal antibodies | One injection for those assigned to AZD3152 will be placebo |
| 4.2.2 Rationale for Study Population | Changed references to AZD5156 to AZD3152 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.3.1 Justification for AZD5156 Dose | Noted that AZD5156 will be administered in the Sentinel Safety Cohort | Clarification |
| 4.3.4 Justification for Placebo | Added details of administration of placebo that will be included with AZD3152 to maintain the blind | One injection for those assigned to AZD3152 will be placebo |
| 4.4 End of Study Definition | Noted that results from some laboratory samples may not become available until after the study completion date | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | AZD3152 is now included | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.1 Randomization | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.2 Blinding | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.2 Blinding | Added AstraZeneca Bioanalytical monitor and unblinded Biometric teams to the list of those who will have access to the randomization list during the study | Clarification |
| 7.1 Discontinuation of Study Intervention | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort, also added clarification about process if participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Noted that AstraZeneca will make the final decision on a temporary hold after analysis of the safety data | Clarification |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Clarified that study would be put on temporary hold if Grade 3 or higher AEs were reported for at least 2 participants (and not simply when 2 Grade 3 or higher AEs were reported) | Wording made consistent with previous AZD7442 studies |
| 8.2.2 Vital Signs | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed) | Clarification regarding the time around vital signs collection |
| 8.2.4 Clinical Safety Laboratory Assessments | Removed reference to Laboratory Manual | Not applicable |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that glucose assessment is specifically glucose (random), and added pregnancy test and FSH to the table of variables | Clarification |
| 8.2.4 Clinical Safety Laboratory Assessments | Added clarifications around pregnancy testing. Furthermore, the FSH evaluation no longer applies only to those in the Sentinel Safety Cohort. | Clarification |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Reiterated that SAEs, MAAEs, and AESIs will be collected throughout the study | Clarification |
| 8.3.4 Adverse Events of Special Interest | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.3.9 Reporting of Serious Adverse Events | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.1 Pharmacokinetics | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.2.1 Anti-drug Antibody Assessments | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.6.2 Other Study-Related Biomarker Research | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.1 General Considerations | Description of study updated to reflect change of strategy in terms of using AZD3152 alone | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.2 Efficacy | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.6 Pharmacokinetics | Order of paragraphs reversed, so that Sentinel Safety Cohort is discussed first, text regarding Main Cohort updated to reference AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Removed text regarding an emerging VOC significantly affecting the neutralization activity of AZD7442 | Updated information, as there is a possibility that the situation described in the deleted text may have already occurred |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.7 Data Safety Monitoring Board – Main Cohort | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

**CSP Version 4.0 [16 January 2023]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to add efficacy as a secondary endpoint to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the Main Cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy of AZD5156 compared with AZD7442. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

The protocol has also been amended to enhance the safety assessments of the Main Cohort, at the request of a Regulatory Authority.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1; noted that the test must return a negative result before dosing | To align with internal guidance for WOCBP |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total) |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Additional assessments of vital signs have been added on Days 8 and 189 of the Main Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Pregnancy test added at Visit 1, with the timing specified as prior to randomization | To align with internal guidance for WOCBP (pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Sample for serum chemistry, hematology, coagulation (local laboratory) will be collected on Days 1, 8, and 29; noted that this assessment is to be performed for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of troponin at screening for the Main Cohort | To increase cardiac safety monitoring |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added the footnote clarifying that home or mobile visits by study staff may substitute for site visits to the Day 1 Illness Visit as well | To ensure sites can perform the Day 1 Illness Visit at home, if needed |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e-Diary and training has been added, along with Investigator site review of e-Diary entry completion | Clarification and for consistency |
| 3 Objectives and Endpoints | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP administration (was previously to Day 29) | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention |
| 3 Objectives and Endpoints | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3 Objectives and Endpoints | References to dominant variants removed | To make the objectives/endpoints less specific |
| 3 Objectives and Endpoints | nAb responses to variant BA.2 will be evaluated | To include current and emerging variants of concern |
| 3 Objectives and Endpoints | Addition of secondary endpoint related to efficacy | Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case will be evaluated as a secondary endpoint |
| 3 Objectives and Endpoints | For the objective '*To characterize the cellular immune responses to SARS-CoV-2*' the following endpoint has been added: *Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing* | To further characterize the cellular immune response |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated. This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total) |
| 4.1 Overall Design | The collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 4.1 Overall Design | Noted that MAAEs will be collected throughout the study | Consistent with added safety endpoint |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #4 has been deleted | Duplication with the original inclusion #7 |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11 (original exclusion #10), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15 (original exclusion #14), hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #3 (original inclusion #4) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on negative rapid antigen test at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #4 (original inclusion #5) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Text regarding participants with cancer in Inclusion #5 (original inclusion #6) has been updated to clarify that those with solid tumor cancer who are included in the study must be on active treatment, excluding the exceptions noted; hematologic malignancy has now been noted as a separate risk factor | This was a Regulatory Authority request |
| 5.2.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12 (original exclusion #11), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Subsection on stopping rules for Main Cohort removed | Replaced with new section on Study Suspension/Early Termination |
| 7.4 Study Suspension/Early Termination | New section | Added for consistency with wording used in AZD7442 studies |
| 8.2.3 Electrocardiograms | New section | Added to describe procedures for ECG |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted that serum chemistry, hematology, coagulation (local laboratory) assessments will be conducted for at least the first 600 participants in the Main Cohort; deleted text stating that clinical safety laboratory assessments will not routinely be performed for the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted (in Table 11) that troponin assessment will be performed in the Main Cohort at screening | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1.1 Determination of Drug Concentration | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.6.2.1 Assessment of Cell-mediated Immune Responses | New section | For consistency with endpoints section |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.7 Data Safety Monitoring Board – Main Cohort | Added MAAEs to the safety parameters that will be assessed as part of the DSMB review | Consistent with MAAEs having been added as a safety endpoint |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Updated footnote to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 1.3 Schedule of Activities | Updated text describing the duration of treatment and follow-up periods from 12 months to 15 months | To reflect the change to the study design to increase the safety collection time |
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Moved the footnote marker for vital signs assessments from dosing days to the overall row header as abnormal vital signs must be repeated at all scheduled vital signs assessments, and not only on dosing days, after the participant has been at rest for at least 5 minutes | Correction for consistency with vital signs assessments for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The numbers of confirmed cases and deaths due to COVID-19 have been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'currently circulating Omicron variants' has been replaced with 'past Omicron variants' | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Specified that cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies | Clarification that these events will be monitored in other AZD5156 studies in addition to the present study |
| 2.3.2 Benefit Assessment | Noted that similarity of AZD5156 to AZD7442 is in terms of structure and mechanism of action | Clarification |
| 2.3.2 Benefit Assessment | Noted that AZD7442 and AZD5156 may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus | Clarification |
| 3 Objectives and Endpoints | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative RT-PCR at baseline to positive at any time up to 6 and 12 months | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 3 Objectives and Endpoints | Minor change to endpoint describing how exploratory samples may be used to align with change in Section 8.5.2.3 | Clarification |
| 4.1 Overall Design | Added that the safety and neutralizing activity of AZD5156 will be compared with AZD7442 for pre-exposure prophylaxis of | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | COVID-19 and that the study will be conducted globally | |
| 4.1 Overall Design | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.1 Overall Design | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1 Overall Design | Added that immediate AEs will be collected for a 1-hour observation period after study intervention administration | Clarification |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Updated text to provide further information on ESDRs | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.2 Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.2 Scientific Rationale for Study Design | Noted that a dose exploration study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.1 Rationale for Administration Site | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions | To further clarify rationale for the administration site |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the threshold (was $IC_{90}$ now $IC_{80}$) | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.1 Inclusion Criteria (Sentinel) | For inclusion #6, clarified that participant must understand and comply with all study requirements/procedures | Clarification |
| 5.2.1 Inclusion Criteria (Main) | For inclusion #7, clarified that participant must understand and comply with all study requirements/procedures (including those at Illness Visits) | Clarification |
| 5.4 Screen Failures | Criteria for rescreening have been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated in the text and in a footnote to Table 8 | Updated to reflect current information |
| 6.1 Study Intervention(s) Administered | Noted in the text and in a footnote to Table 8 that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive the first component of their assigned intervention will all receive the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Added specific details for placebo | Clarification |
| 6.1 Study Intervention(s) Administered | Noted in Table 8 that L-histidine hydrochloride is monohydrate | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage and administration of IMP | Wording added to provide more comprehensive details of IMP storage and administration |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.1 Randomization | Added text that participants will receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention, and those having access to the randomization list during the study | Clarification |
| 6.3.2 Blinding | Removed text about Investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.5 Concomitant Therapy | Minor update to wording regarding the Concomitant Medication eCRF | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the 'Restricted' section in Table 9 | To ensure the correct patient population is enrolled |
| 8 Study Assessments and Procedures | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 8.1.2 Participant-reported COVID-19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | Extra information added regarding e-Diaries and documentation in the eCRF | Updated for clarity |
| 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments | Added text stating that genotypic sequencing analysis and phenotypic characterization would be of SARS-CoV-2 Spike protein mutations rather than of the virus | Clarification |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment, and noted that any observations will | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | be documented in the participant's medical records | |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 8.2.4 Clinical Safety Laboratory Assessments | Included the option for urea results to be reported as blood urea nitrogen, and for prothrombin time results to be reported as international normalized ratio | Clarification |
| 8.2.5.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.5.2 Injection Site Reactions | Noted that diameters of any redness/swelling may be recorded at site visits | Clarification |
| 8.2.5.2 Injection Site Reactions | Removed references to specific time points for the Sentinel Safety Cohort | Those specific details were not needed because reference is made to the SoAs |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Noted that AESIs will be programmatically identified through AE information that is collected in the eCRF | Clarification |
| 8.3.4 Adverse Events of Special Interest | Minor edits made throughout the section | Updated for clarity |
| 8.3.9 Reporting of Serious Adverse Events | Minor change to wording of statement about reporting of SAEs | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.3.11.1 Timelines | Updated wording for SAEs associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.2.3 Additional Serum Immunogenicity | Minor change to statement regarding how exploratory serum samples may be used | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.3 Populations for Analyses | Updated the definition of the SARS-CoV-2 neutralizing antibody analysis set to remove the text 'with quantifiable SARS-CoV-2 serum titers' | This was a Regulatory Authority request related to the inclusion of participants without quantifiable serum titers but who received investigational product |
| 9.3 Populations for Analyses | Updated the definition of the anti-drug antibody analysis set | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.1 General Considerations | Noted that details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses | Clarification |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.4.2 Efficacy | Deleted reference to 'incidence of post treatment COVID-19' as 'incidence of post treatment symptomatic COVID-19' is already specified | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 9.4.4 Anti-drug Antibody Variables | Text regarding anti-drug antibody variables edited, with a reference added to the SAP | To simplify the text to keep the necessary information and refer to the SAP for further details |
| 9.5 Planned Analyses | Added details of analyses for Sentinel Safety Cohort | Clarification |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | team will remain blinded during primary analysis | |
| 9.5 Planned Analyses | Noted that an evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID 19 be observed prior to the final analysis | Clarification |
| 9.7 Data Safety Monitoring Board – Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore, have not been summarized |

**CSP Version 3.0 [09 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort, at the request of a Regulatory Authority.

**Summary of Changes**:

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory | This has been added to assist with making a decision regarding whether a female participant is |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | assessments at screening for the Sentinel Safety Cohort | postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination, vital signs, and injection site reaction monitoring (local reactogenicity) have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Sample for clinical safety laboratory assessments added at Day 1 (predose) for the Sentinel Safety Cohort | To obtain baseline values |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For the vital signs assessment on Day 1 of the Sentinel Safety Cohort, the indicator '(predose)' has been deleted | This has been deleted for reasons of clarity, because Day 1 vital signs are not only assessed predose, and the existing footnote (a) provides specific details of the timings |

**CSP Version 2.0 [02 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

Note: due to a typing error, the word 'imitating' appears several times instead of 'initiating' in this historical Summary of Changes, and reference is made to the fact that '*no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed*'; this should have read 80 adult Main Cohort participants.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | AZD5156/AZD3152 |
| Study Code | D7000C00001 |
| Version | 8.0 |
| Date | 21 Dec 2023 |

# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version Number: 8.0

Study Intervention:

*Sentinel Safety Cohort*
AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152), or placebo (0.9% sodium chloride for injection)

*Main Cohort*
AZD3152 monoclonal antibody or placebo (0.9% sodium chloride for injection)

*Sub-study*
AZD3152 monoclonal antibody or AZD7442 (EVUSHELD), the active comparator

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Brief Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 8.0 | 21-Dec-2023 |
| CSP Version 7.0 | 14-Jun-2023 |
| CSP Version 6.0 | 24-May-2023 |
| CSP Version 5.0 | 07-Feb-2023 |
| CSP Version 4.0 | 16-Jan-2023 |
| CSP Version 3.0 | 09-Dec-2022 |
| CSP Version 2.0 | 02-Dec-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 8.0 [21 December 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended to address the changing variant landscape by adding a second (dual) primary endpoint to the SUPERNOVA study (Main Cohort) to estimate efficacy in matched variants (variants that do not contain the F456L mutation and are expected to be susceptible to AZD3152).

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis<br>3. Objectives and Endpoints<br>9.1 Statistical Hypotheses | Added second primary efficacy endpoint for the Main Cohort and updated the population for the primary endpoints from Full Analysis set to SARS-CoV-2 Negative set | To address the changing variant landscape, efficacy for matched variants was added as a primary endpoint together with all variants efficacy endpoint |
| 1.1 Synopsis<br>3. Objectives and Endpoints | Added text to primary efficacy endpoint definition as "Confirmed symptomatic COVID-19 case, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19" | For clarification |
| 1.1 Synopsis<br>3. Objectives and Endpoints<br>9.4.2.3 Secondary Efficacy Endpoints | Added text to include all confirmed events and all matched variant events in the secondary endpoints for post treatment incidence of symptomatic COVID-19 cases and severe COVID-19 | To account for matched variant endpoint that was added to the primary endpoint |
| 4.2.4 Rationale for Dual Primary Efficacy Endpoint for the Main Cohort | A new subsection has been added to provide a justification for adding the matched variant analysis as second primary efficacy endpoint | Justification for the addition of a dual primary efficacy endpoint |
| 9.1 Statistical Hypotheses | Added text to specify two separate null hypothesis tests by using the Holm step-down procedure | To update statistical testing methods for both primary endpoints |
| 9.2 Sample size determination | Added text and two new tables providing details of assumptions for the dual efficacy endpoints with varying levels of AZD3152 resistance to achieve at least 90% power with the current enrollment target | Justification required due to addition of dual primary efficacy endpoint |
| 9.3 Populations for Analyses | Added definition for SARS-CoV-2-negative analysis set | To clarify how baseline PCR results will be used |
| 9.4.2 Efficacy | Added a subsection to include the efficacy analysis methodology for the primary matched variant endpoint | To cover statistical analysis of second dual primary endpoint |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis<br>9.5 Planned Analyses | Updated double-blind period maintenance status based on the SARS-CoV-2-Negative Set and the required number of events observed for dual primary efficacy endpoints.<br><br>Updated number of events required for primary analysis which will be based on prevalence of resistant events | For clarification |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1. Synopsis,<br>8.3.4 Adverse Events of Special Interest<br>9.8 Cardiovascular Event Adjudication Committee | A Cardiovascular Event Adjudication Committee has been added | To provide an independent, external, systematic, and unbiased assessment of de-identified blinded data to systematically evaluate CV events |
| 1.1 Synopsis<br>3. Objectives and Endpoints<br>9.4.2.1 Primary Confirmed Symptomatic COVID-19 Endpoint | Revised follow-up time in days instead of months (181 Days & Day 361) for confirmed symptomatic COVID-19 case after last dose in both primary efficacy endpoints<br><br>Added text to clarify that both efficacy endpoints will be classified as a binary outcome and analyzed by using survival methodology<br><br>Rephrased the definition of intercurrent events for primary all event endpoint analysis to align with wording of intercurrent events for matched variant endpoint analysis | For clarification<br><br>For consistency between dual primary efficacy endpoints |
| 1.2 Schema<br>4.1.2 Main Cohort | Added a new footnote “the Main Cohort Placebo arm also contains participants that were dosed with AZD7442 prior to the implementation of Clinical Study Protocol version 7.0” | To clarify the Placebo arm also contains AZD7442 prior to CSP v7 implementation |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Re-labeling of footnote within the table related to the "Weekly telephone/email/text contacts monitoring for safety and COVID 19 qualifying symptoms" | In error, footnote (l) was associated with this assessment; it should be footnote (m) ("Weekly [prior to Day 361] and then monthly [from Day 361] contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms |
| | Deleted text from footnote (m) "The weekly and monthly telephone/email/text contacts should be performed in addition to any scheduled site visits." | To add clarity that a telephone call contact is not required if a participant had an on-site visit that week |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>4.1 Overall Design<br>8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Deleted text from footnote (n) "but do not prompt an illness visit" | To provide clarity that COVID-19 related AEs that do prompt an Illness Visit (eg, symptomatic COVID-19) will be collected in the eCRF |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Replaced '±' for illness Day 5 (IL-D5) with '+' | Revised to stop potential combining of IL-D3 & IL-D5 as there are ± on both illness days eg, both visits could occur on Day 4 |
| 2.2.2 AZD5156, AZD3152, and EVUSHELD | The term 'all known SARS-CoV-2 viral variants' has been replaced with 'circulating SARS-CoV-2 viral variants' | This information has been brought up to date |
| 2.2.2 AZD5156, AZD3152, and EVUSHELD | Revised text to remove 'potency against all the Omicron variants' to 'many Omicron variants' (eg, BQ.1.1, XBB.1.5, XBB.2.3) | To add clarity since AZD3152 is not working against all variants |
| 5.2.2 Exclusion Criteria<br>5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5<br>6.5 Concomitant Therapy | Replaced text 'IV and SC' to 'IV or SC' for eligibility criteria | For consistency |
| 9.2 Sample size determination | Added text to sample size determination for Main Cohort | To clarify the target enrollment has not changed by including additional primary endpoint |
| 9.5 Planned Analyses | Added Visit 9 (Day 181) completion for Sentinel Safety Cohort participants | For clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.4.2.3 Secondary Efficacy Endpoints | Replaced word ‘derived as’ with ‘classified as’ | For clarification |
| 9.5 Planned Analyses | Added Visit 9 (Day 181) completion for Sentinel Safety Cohort participants | For clarification |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| CV | Cardiovascular |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| FAS | Full analysis set |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |

| Abbreviation or special term | Explanation |
|---|---|
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GMFR | Geometric Mean Fold Rise |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| hCG | Human chorionic gonadotropin |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{50}$ | Concentration giving half-maximal inhibition |
| $IC_{80}$ | Concentration required for 80% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IVIG | Intravenous immunoglobulins |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |

| Abbreviation or special term | Explanation |
|---|---|
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SCIG | Subcutaneous immunoglobulins |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study. The main part of this CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum to the CSP.

In the Parent study, the Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442 (EVUSHELD)] and AZD3152) in healthy adults and the Phase III Main Cohort will assess the safety, efficacy, PK, and neutralizing activity of two doses of AZD3152 compared with two doses of comparator given at a 6-month interval in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19.

Prior to CSP v7.0, the comparator for the Main Cohort was EVUSHELD as the immunobridging portion of the study was incorporated into the Parent study. At the request of regulatory authorities, a sub-study specifically for immunobridging is being undertaken (which will be conducted in the US only). As a result, the Parent study will become an efficacy and safety study, and the comparator will therefore be changed to placebo. As the comparator is given on two occasions, this means that a participant randomized to the comparator arm may receive (a) two doses of EVUSHELD, (b) a dose of EVUSHELD and a dose of placebo, or (c) two doses of placebo.

The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and EVUSHELD.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through approximately 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA to AZD5156, AZD3152, and AZD1061, ADA titers |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and EVUSHELD and/or placebo | Occurrence of AEs collected through approximately 90 days after each IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant | **Population**: SARS-CoV-2-Negative Set<br>**Endpoint**: Confirmed symptomatic COVID-19 case, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as:<br>• Positive post-baseline RT-PCR at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention prior to having met the criteria for the COVID-19 endpoint. Such participants will be censored at the earliest of the following:<br>• The date of unblinding<br>• Receipt of the first dose of any COVID-19 preventive product<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus EVUSHELD and/or placebo) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID 19 attributable to matched variants (variants that do not contain the F456L mutation) | **Population**: SARS-CoV-2-Negative Set<br>**Endpoint**: Confirmed symptomatic COVID-19 case attributable to matched variants, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as:<br>• Positive post-baseline RT-PCR at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND<br>• Satisfying the modified WHO definition of symptomatic COVID-19 AND<br>• Viral sequencing from associated positive RT-PCR is attributable to matched variants<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention prior to having met the criteria for the COVID-19 endpoint. Additionally, RT-PCR-confirmed symptomatic COVID-19 infections that are either unrelated to matched variants or undetermined variants will be considered intercurrent events. Such participants will be censored at the earliest of the following:<br>• The date of unblinding<br>• Receipt of the first dose of any COVID-19 preventive product<br>• Date of first occurrence of an RT-PCR-confirmed symptomatic COVID-19 case not attributable to a matched variant<br>**Analysis strategy**: While-on-treatment strategy – participants will be analyzed according to randomized treatment and censored at the time of the earliest intercurrent event prior to having met the criteria for the endpoint.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus EVUSHELD and/or placebo) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Secondary (Main Cohort)** | |
| To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and EVUSHELD and/or placebo administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29)<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months) caused by any SARS-CoV-2 variant<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months) caused by any SARS-CoV-2 matched variants<br>• Severe COVID-19 caused by any SARS-CoV-2 variant<br>• Severe COVID-19 caused by any SARS-CoV-2 matched variants<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study that will be conducted in approximately 3706 participants (approximately 3256 in the Parent study and 450 in the sub-study) to evaluate the safety, efficacy, PK, and neutralizing activity of AZD3152 compared with EVUSHELD or placebo for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum.

The Parent study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with placebo.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (ie, active treatment or comparator) 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and EVUSHELD use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded to study intervention).

**Number of Participants:**

Approximately 3256 participants will be randomized in the Parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be

randomized 1:1 to receive AZD3152 or comparator.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: 1 dose of AZD3152 300 mg IM or comparator (on 2 occasions with a 6-month interval).

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Sentinel Safety Cohort as follows: after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b), and subsequently after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 subcohorts, prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

**Cardiovascular Event Adjudication Committee:**

For the Main Cohort only, an independent cardiovascular (CV) Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of blinded data to systematically evaluate CV events. A separate charter will define the scope of the CV Event Adjudication Committee.

**Statistical Methods**

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will

correspond to a 2-sided test unless otherwise stated.

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK concentrations at Day 29. The remaining two analyses will include all available data when conducted. The study will maintain a double-blind period until a median follow-up time is greater than 181 days in the SARS-CoV-2-Negative Set and the required number of events are observed for the dual primary endpoints to support the primary efficacy and safety objectives and trigger the primary analysis. The exact number of events required for the primary analysis will be based on the prevalence of resistant events (variants with F456L mutation) within the study and will be documented in the SAP. If it is unlikely that sufficient events will be observed for either endpoint or all participants have been followed for more than 361 days or withdrawn from the study, the database will be locked for primary analysis.

Participants randomized to the comparator arm in the Main Cohort may have received doses of EVUSHELD or placebo at either first or second IMP administration and will be presented as a combined comparator study arm for the efficacy evaluation. Safety data will be summarized by each comparator group (EVUSHELD or placebo) separately and combined. When appropriate, actual dose(s) received may be presented separately to the combined comparator group. Any participant who received or was assigned to EVUSHELD at the first or second IMP dose will be presented as having received or been assigned to EVUSHELD. The SAP will provide details on the presentation of data by assigned and actual treatments received.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD3152 and comparator and to compare the efficacy of AZD3152 versus comparator in the Main Cohort for the prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant and symptomatic COVID-19 caused by SARS-CoV-2 matched variants. Separately, safety and PK of AZD5156 will be evaluated in the Sentinel Safety Cohort.

Both symptomatic COVID-19 attributable to any variant and symptomatic COVID-19 attributable to matched variants efficacy endpoints are classified as a binary outcome and analyzed using survival methodology. The analysis incorporates the time in days from IMP administrations until a participant develops their first symptoms for COVID-19 at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations). Positive cases require a central RT-PCR test and meet the qualifying symptoms as indicated by the Investigator satisfying the modified WHO definition of symptomatic COVID-19. The analysis will be based on the SARS-CoV-2-negative analysis

set. The symptomatic COVID-19 attributable to any variant and symptomatic COVID-19 attributable to matched variants efficacy endpoints will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to compare prophylactic efficacy (ie, 1-HR) of AZD3152 versus comparator.

Adverse events and SAEs will be coded using the most recent version of MedDRA, where possible, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

Efficacy Endpoints

The secondary COVID-19 efficacy endpoints are classified as a binary outcome. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point based on the SARS-CoV-2-negative analysis set.

SARS-CoV-2 nAb Response

The secondary endpoints of nAb responses against SARS-CoV-2 variants, including Alpha, Omicron BA.2, Omicron BA.4/5 and Omicron XBB.1.5 will be evaluated using the geometric mean titer (GMT) ratio between treatment arms. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152.

Characterization of PK

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of these 2 component mAbs of AZD5156. The following single dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or EVUSHELD, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Evaluation of ADA

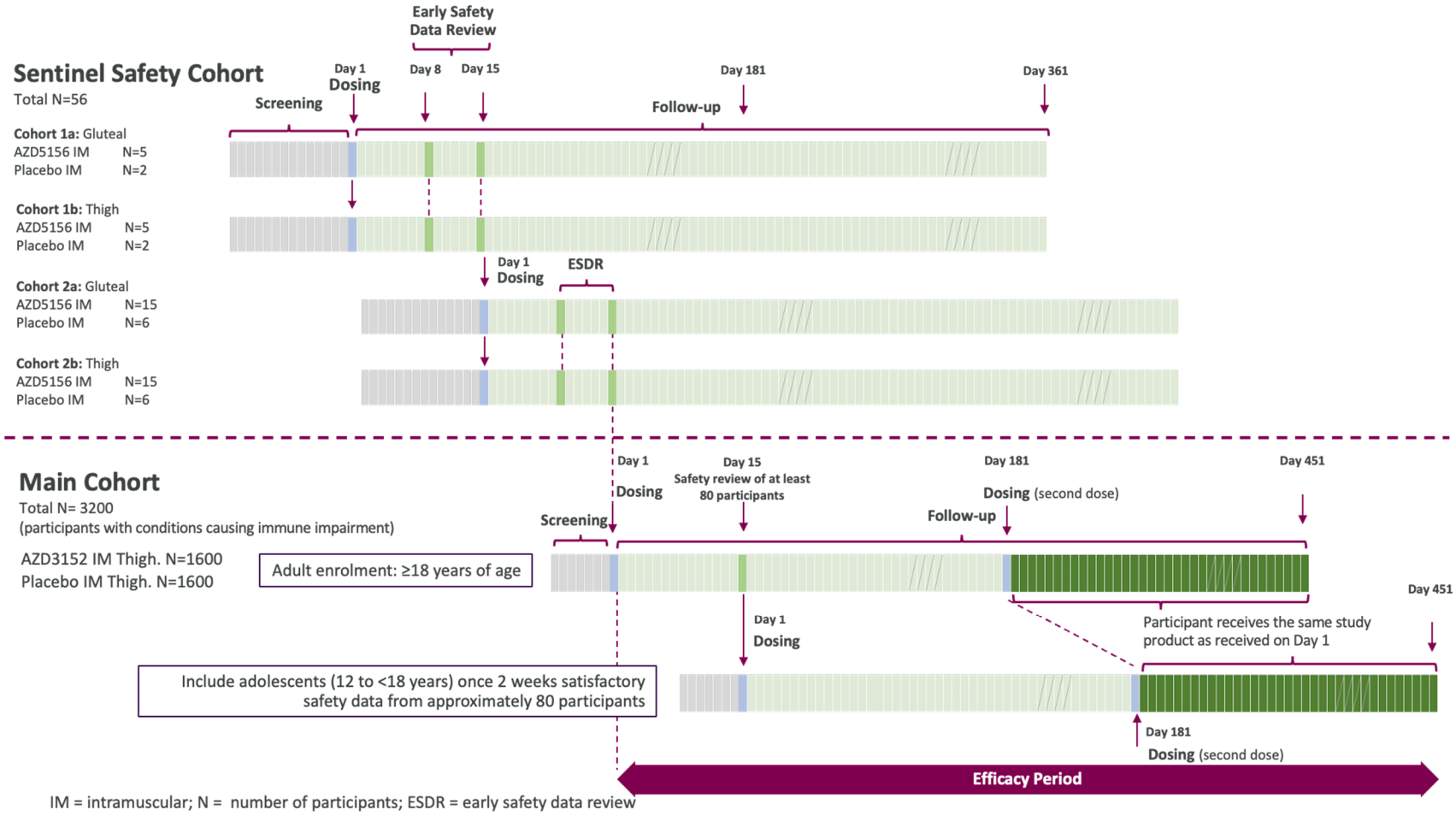
The ADA variables will be assessed and summarized by number and percentage of

participants by treatment group based on the respective ADA analysis set. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort (data up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b), and then prior to enrollment of the Main Cohort.
Note: Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed.
Note: The Main Cohort Placebo arm also contains participants that were dosed with AZD7442 prior to the implementation of Clinical Study Protocol version 7.0.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 14 days (Day -14 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| 12-Lead electrocardiogram (single, to be performed locally) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [f] | X | X | X | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | | | | | | | |
| Verify selected eligibility criteria for receipt of second dose (Visit 5) [c] | | | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | Weight only (predose) | | | | | | X [d] |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [e] | X | X | X | | | | X | X | | | | | |
| 12-lead electrocardiogram (single, to be performed locally) | X | | | | | | | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Urine or serum β-hCG pregnancy test (WOCBP only, performed locally) [f] | X | X (predose) | | | | | X (predose) | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [g] | | X (predose) | | | | | X [h] (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [i] (predose) | | | | | X [i] (predose) | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) [j] | | X (predose) | X | | X | | | | | | | | |
| Troponin T or I (local laboratory) | X [k] | | | | | | | | | | | | |
| Follicle stimulating hormone [l] | X | | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [m] | | X ← → | | | | | | | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b [a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Monthly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [m] | | | | | | | | | | | ◄——► | | |
| Assessment of AEs [n] | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |
| PK serum sample [o,p] | | X (predose) | | | X | X | X (predose) | X | X | | X | | |
| PK nasal lining fluid sample [q] | | X (predose) | | | X | X | | | | | | | |
| ADA and anti-drug nAbs assessment serum sample [o] | | X (predose) | | | X | X | X (predose) | | X | | X | | |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample [r] | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |

## Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b** [a] | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** [b] | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [s] | X | | | | X [s] | X | | | | | |
| Immediate AEs [t] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] See Section 5.2.3 for the eligibility criteria for the receipt of the second dose of study intervention at Visit 5.
[d] Excludes height measurement in adults aged 18 years and older.
[e] On dosing days, vital signs will be performed predose and again 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[f] Sample urine or serum β-hCG pregnancy test must return a negative result before dosing. Pregnancy testing prior to each dose must be on the same day as dosing and is especially important for female participants who had not reached menarche on enrollment into the study.
[g] Sites will be provided with rapid antigen tests.
[h] If a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3).
[i] To be collected at baseline. The results are not needed prior to dosing.
[j] To be performed for at least the first 600 participants in the Main Cohort.
[k] It is acceptable for this to be performed on Day 1 (predose).
[l] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[m] Weekly (prior to Day 361) and then monthly (from Day 361) contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[n] Adverse events that occur outside of the 90-day window between each study intervention administration that are either related to IMP, or are COVID-19-related (eg, asymptomatic COVID-19), will be reported on the AE CRF page.
[o] Samples will only be collected and analyzed for the first 1200 participants (approximately) in the Main Cohort.
[p] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.

[q] Samples collected only for the first 600 participants (approximately) in the Main Cohort.
[r] Samples will be prioritized for PK and ADA/nAb analysis as needed.
[s] Perform immediately, 30 minutes (+ 10 minutes) and 1 hour after both injections are complete, and prior to participant release.
[t] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable.

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; β-hCG = beta human chorionic gonadotropin; CRF = case report form; EDV = Early Discontinuation Visit; IMP = investigational medicinal product; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Unscheduled Visit** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|---|
| **Day [c]** | | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | | **NA** | **± 1** | **+ 1** | **± 1** | **± 1** | **+ 2** |
| Verify qualifying clinical symptoms [d] | X | | | | | | |
| Medical history | | X | | | X | | X |
| Targeted physical examination | | X | | | X | | X |
| Vital signs (including pulse oximetry) | | X | | | X | | X |
| Set up of e-Diary and training | | X | | | | | |
| Assessment of AEs, SAEs, MAAEs, and AESIs | | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily for 14 days by participant in Illness e-Diary) | | X ◄——————————————————————► | | | | | |
| Investigator site review of e-Diary entry completion | | X (ongoing) | | | | | |
| Saliva sample for viral shedding | | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | | X | | | X | | X |
| PBMCs for T-cell responses | | X | | | X | | X |
| PK serum sample | | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Unscheduled Visit** | **Site [b]** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|---|
| **Day [c]** | | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | | **NA** | **± 1** | **+ 1** | **± 1** | **± 1** | **+ 2** |
| SARS-CoV-2 neutralizing antibody serum sample | | X | | | X | | X |
| Exploratory analysis serum sample | | X | | | X | | X |
| Telephone contact for safety monitoring [f] | | | X | X | | X | |
| WHO Clinical Progression Scale [f] | | X | X | X | X | X | X |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit Day 1 = 1IL-D1, Illness Visit Day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] If the participant meets the clinical criteria adapted from the WHO COVID-19 case definition (see Section 8.1.2), then an illness visit (IL-D1) will be initiated.

[e] A local and central RT-PCfR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results may not be reported to sites during the Illness Visit period.

[f] For the duration of the Illness Visit period, sites should follow-up with the participant either at the site visit or by telephone for home visits to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19.

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study. The main part of this CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum to the CSP.

In the Parent study, the Phase I Sentinel Safety Cohort will assess the safety of AZD5156 (a combination of 2 mAbs, AZD1061 [cilgavimab, a component of AZD7442 (EVUSHELD)] and AZD3152) in healthy adults and the Phase III Main Cohort will assess the safety, efficacy, PK, and neutralizing activity of two doses of AZD3152 compared with two doses of comparator given at a 6-month interval in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19.

Prior to CSP v7.0, the comparator for the Main Cohort was EVUSHELD as the immunobridging portion of the study was incorporated into the Parent study. At the request of regulatory authorities, a sub-study specifically for immunobridging is being undertaken (which will be conducted in the US only). As a result, the Parent study will become an efficacy and safety study, and the comparator will therefore be changed to placebo. As the comparator is given on two occasions, this means that a participant randomized to the comparator arm may receive (a) two doses of EVUSHELD, (b) a dose of EVUSHELD and a dose of placebo, or (c) two doses of placebo.

The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and EVUSHELD. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of COVID-19 that, as of 31 May 2023, has caused over 767 million confirmed cases of COVID-19, including more than 6.9 million deaths, reported to the WHO (WHO 2023). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated continued development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 AZD5156, AZD3152, and EVUSHELD

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including EVUSHELD. The potency of EVUSHELD was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against some of the more recent Omicron variants such as BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the

prevention of symptomatic COVID-19 that neutralizes circulating SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease. AZD3152 was initially developed to provide efficacy similar to that of EVUSHELD but with greater breadth against variants not potently neutralized by EVUSHELD.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of EVUSHELD with greater neutralization potency against the past Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to EVUSHELD, specifically high neutralizing potency against many Omicron variants against which EVUSHELD lost activity (eg, BQ.1.1, XBB.1.5, XBB.2.3).

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of EVUSHELD in vitro. Given both AZD3152 and EVUSHELD target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD3152 builds upon the established safety and efficacy of EVUSHELD. AZD3152 is expected to have a similar safety and PK profile and broader efficacy against a wider range of SARS-CoV-2 VOCs than EVUSHELD.

It is considered reasonable that AZD3152 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD3152 are similar to those of the component mAbs of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, BF.7, XBB, and XBB.1 for AZD3152 are superior to those of AZD7442.
- EVUSHELD has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the

pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD3152 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD3152 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 and AZD3152 are provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with EVUSHELD, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the EVUSHELD mAb combination product. Overall, the structural similarities between AZD5156 and EVUSHELD suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of EVUSHELD; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 and AZD3152 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations

such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156/AZD3152 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. This is not expected with AZD5156 or AZD3152 because, similar to EVUSHELD, they have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the EVUSHELD program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the EVUSHELD arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of CV disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other EVUSHELD clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between EVUSHELD and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 and AZD3152 studies.

### 2.3.2 Benefit Assessment

AZD5156 and AZD3152 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline as shown in the Phase III PROVENT trial (Levin et al 2022). It should be noted that the comparator EVUSHELD, as well as AZD3152 and AZD5156, may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD3152 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Overall, it is considered that the AZD5156 and AZD3152 nonclinical data available to date, and clinical data from similar mAbs, including EVUSHELD, provide confidence that the overall benefit-risk is favorable.

Detailed information about the known and expected benefits and potential risks of AZD5156/AZD3152 and EVUSHELD is provided in the respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary (Sentinel Safety Cohort)** | |
| To evaluate the safety of AZD5156 | Occurrence of AEs collected through approximately 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| **Secondary (Sentinel Safety Cohort)** | |
| To characterize the PK of AZD5156 and AZD3152 in serum | AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$) |
| To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum | Incidence of ADA to AZD5156, AZD3152, and AZD1061, ADA titers |
| **Primary (Main Cohort)** | |
| To evaluate the safety of AZD3152 and EVUSHELD and/or placebo | Occurrence of AEs collected through approximately 90 days after each IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant | **Population**: SARS-CoV-2-Negative Set<br>**Endpoint**: Confirmed symptomatic COVID-19 case, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as:<br>• Positive post-baseline RT-PCR at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| | participants who receive both planned treatment administrations) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention prior to having met the criteria for the COVID-19 endpoint. Such participants will be censored at the earliest of the following:<br>• The date of unblinding<br>• Receipt of the first dose of any COVID-19 preventive product<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus EVUSHELD and/or placebo) using a hazard regression model. |
| To compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID 19 attributable to matched variants (variants that do not contain the F456L mutation) | **Population**: SARS-CoV-2-Negative Set<br>**Endpoint**: Confirmed symptomatic COVID-19 case attributable to matched variants, classified as a binary outcome incorporating the time from the first dose of IMP until a participant develops their first symptoms for COVID-19, which is defined as:<br>• Positive post-baseline RT-PCR at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND<br>• Satisfying the modified WHO definition of symptomatic COVID-19 AND<br>• Viral sequencing from associated positive RT-PCR is attributable to matched variants<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other non-investigational product(s) for COVID-19 prevention prior to having met the criteria for the COVID-19 endpoint. Additionally, RT-PCR-confirmed symptomatic COVID-19 infections that are either unrelated to matched variants or undetermined variants will be considered intercurrent events. Such participants will be censored at the earliest of the following:<br>• The date of unblinding<br>• Receipt of the first dose of any COVID-19 preventive product<br>• Date of first occurrence of an RT-PCR-confirmed symptomatic COVID-19 case not attributable to a matched variant<br>**Analysis strategy**: While-on-treatment strategy – |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| | participants will be analyzed according to randomized treatment and censored at the time of the earliest intercurrent event prior to having met the criteria for the endpoint.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD3152 versus EVUSHELD and/or placebo) using a hazard regression model. |
| **Secondary (Main Cohort)** | |
| To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and EVUSHELD and/or placebo administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29)<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months) caused by any SARS-CoV-2 variant<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months) caused by any SARS-CoV-2 matched variants<br>• Severe COVID-19 caused by any SARS-CoV-2 variant<br>• Severe COVID-19 caused by any SARS-CoV-2 matched variants<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD3152 and AZD7442 in serum | AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD3152 and AZD7442 in serum | Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers |
| **Exploratory** | |
| To assess the PK of AZD5156, AZD3152, and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD3152 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD3152 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |

**Table 5 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| | Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered EVUSHELD and AZD3152 | Other exploratory assays for humoral, mucosal, and cellular immune responses, including additional SARS-CoV-2 nAb, may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |
| To characterize the predicted serum nAb responses to SARS-CoV-2 variants following IMP administration | Descriptive statistics for predicted GMTs will include the number of participants, geometric mean, gSD, 95% CI, summarized by treatment arm and visit for select SARS-CoV-2 variants using PK and in-vitro $IC_{50}$ values [a] |

[a] $IC_{50}$ values from prior in vitro analysis of AZD3152 and AZD7442 in research grade pseudovirus neutralization assays will be used.

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; $IC_{50}$ = concentration giving half-maximal inhibition; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization.

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study (Parent study) being conducted in conjunction with a Phase II sub-study that will be conducted in approximately 3706 participants (approximately 3256 in the Parent study and 450 in the sub-study) to evaluate the safety, efficacy, PK, and neutralizing activity of AZD3152 compared with EVUSHELD or placebo for pre-exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061. The study will be conducted globally. The main part of the CSP refers to the Parent SUPERNOVA study only, and all details for the sub-study are described in an Addendum. The objectives of the sub-study are to evaluate the safety, PK, and predicted neutralizing activity of AZD3152 and AZD7442.

The Parent study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with placebo, while the Main Cohort will compare AZD3152 (one of the components of AZD5156) with placebo.

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Cohort will be applicable to AZD3152 administered alone.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive a single dose of study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable (for more details on the safety review, see Section 4.1.1). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort (Phase III) will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at higher risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152) have been reviewed by the DSMB to determine that there are no safety

issues.

Prior to CSP v7.0, the comparator for the Main Cohort was EVUSHELD as the immunobridging portion of the study was incorporated into the Parent study. At the request of regulatory authorities, a sub-study specifically for immunobridging is being undertaken (which will be conducted in the US only). As a result, the Parent study will become an efficacy and safety study, and the comparator will therefore be changed to placebo. As the comparator is given on two occasions, this means that a participant randomized to the comparator arm may receive (a) two doses of EVUSHELD, (b) a dose of EVUSHELD and a dose of placebo, or (c) two doses of placebo.

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (ie, active treatment or comparator) 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and EVUSHELD use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. For the Main Cohort, AEs that occur outside of these windows between each administration that are either related to IMP, or are COVID-19 related (eg, asymptomatic COVID-19), will be reported on the AE CRF page. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, they will be required to contact the site as soon as possible and the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (adapted from the WHO COVID-19 case definition WHO 2022) and will need to conduct Illness Visits within 3 days after the participant has reported such symptoms (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate

sampling will not be required as detailed in the Laboratory Manual). Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants in the Sentinel Safety and Main Cohorts should refrain from receiving SARS-CoV-2 vaccines until after the Day 29 assessments have been completed. For participants in the Main Cohort, SARS-CoV-2 vaccines should not be given 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first approximately 56 participants in the study will comprise the Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Comparator Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants.

The ESDRs for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- Enrollment will be paused once 14 participants have been recruited in the initial cohorts (1a and 1b). Initial ESDRs will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDRs, enrollment of participants will continue to be paused until after Day 15. If the ESDRs conclude that the safety profile is acceptable, then enrollment will be permitted to continue, and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.

- Enrollment will be paused once more when 42 participants have been recruited into the final 2 cohorts (2a and 2b). Further ESDRs will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile. There is not expected to be any difference in safety profile between AZD3152 administered in combination with AZD1061 (as AZD5156) or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

The safety data collected will be entered into eCRFs and reviewed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDRs:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include at least 40 participants who have received AZD3152).

Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg or comparator administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (ie, active treatment or comparator) 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Comparator Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD3152 300 (1600) | Comparator* (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

* The Main Cohort Placebo arm also contains participants that were dosed with AZD7442 prior to the implementation of Clinical Study Protocol version 7.0.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Section 4.1.1.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous EVUSHELD Phase I study in pre-exposure prophylaxis (D8850C00001) and the EVUSHELD Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and efficacy.

A separate dose exploration study (D7000C00004) will be conducted to evaluate the safety and pharmacokinetics of AZD3152.

Participants in the Main Cohort will be randomized to AZD3152 (instead of the originally planned AZD5156) or placebo. The initial development plan for AZD5156 focused on a combination of two mAbs (cilgavimab [AZD1061] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered EVUSHELD by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering EVUSHELD in the gluteal region in a clinic setting and in obese individuals. Thus, off-label use of EVUSHELD administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration.

Main Cohort participants will all receive study intervention in the anterolateral thigh to

decrease variability in the PK and nAb analyses.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the EVUSHELD Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the main target population using EVUSHELD) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at higher risk of severe COVID-19. The inclusion criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for EVUSHELD, which includes the adolescent population despite not being included in the pivotal Phase III studies. Given the expected safety and PK profile of AZD3152, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD3152 clinical development plan. The adolescent population was approved for EVUSHELD based on PK extrapolation.

### 4.2.3 Rationale for Use of Placebo as Comparator for the Main Cohort

When the study was initially designed, based on the known efficacy of EVUSHELD at that time, AstraZeneca considered EVUSHELD a more appropriate comparator for the Main Cohort than placebo. However, as the Parent study is now primarily an efficacy and safety study, as of CSP v7.0 the comparator for the Main Cohort will be placebo to facilitate feasibility and in compliance with regulatory advice.

### 4.2.4 Rationale for Dual Primary Efficacy Endpoint for the Main Cohort

Due to the changing variant landscape, a second (dual) primary endpoint (matched variant analysis) was introduced into the study. Matched variants are defined as variants that do not contain the F456L mutation and are expected to be susceptible to AZD3152. Addition of the second (dual) primary endpoint is based on the following rationale:

- Variants have constantly changed over time and therefore, the relevant clinical question at the time of prescribing is the level of AZD3152 efficacy against circulating susceptible variants and their prevalence.

- The overall efficacy demonstrated in SUPERNOVA by including all events can be

negatively impacted by periods of high prevalence of resistant variants circulating during the efficacy study period.

- An endpoint based on all events observed during the study's conduct may not be generalizable to subsequent periods as the proportion of susceptible and resistant variants is expected to change significantly over time.

- The dual endpoint addresses the clinical question of AZD3152 efficacy against susceptible variants while still assessing efficacy against all events.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in the Sentinel Safety Cohort of this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for EVUSHELD. Similar PK for AZD5156 and EVUSHELD have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as EVUSHELD, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD3152 Dose

The AZD5156 600 mg dose comprises AZD3152 300 mg and AZD1061 300 mg; therefore, AZD3152 300 mg will be used as the dose in the study (see Section 4.3.1). A 300 mg dose of AZD3152 is predicted to maintain nasal lining fluid concentrations of AZD3152 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.3 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals in the Sentinel Safety Cohort at low risk of development of severe COVID-19 in order to provide a blinded comparison and to allow objective assessment of the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the EVUSHELD Phase I study (D8850C00001).

In the Main Cohort, placebo will also be used as the comparator for AZD3152 (see Section 4.2.3).

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol-related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

The results from some laboratory samples may not become available until after the study completion date.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator,

with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).

2 Age 18 to 55 years at the time of signing the informed consent.

3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.

4 Negative rapid antigen test at Visit 1.

5 Weight ≥ 45 kg and ≤ 110 kg at screening.

6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last

dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN at screening.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test prior to dosing at Visit 1.

4 Weight ≥ 40 kg at screening.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have solid tumor cancer and be on active immunosuppressive treatment
- Have hematologic malignancy

- Transplant participants must satisfy at least one of the following:
  - Have had a solid organ transplant within 2 years and / or
  - Had a hematopoietic stem cell transplant within 2 years and / or
  - Who have chronic graft-versus-host disease
  - Participants who previously had a solid organ transplant or hematopoietic stem cell transplant more than 2 years prior to Visit 1 may also be eligible based on the inclusion criterion for immunosuppressive treatment
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks]), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive biologic agents (eg, for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary (eg, DiGeorge syndrome) or secondary (eg, hemodialysis) immunodeficiency
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts < 200/mm$^3$ within 6 months of Visit 1, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)

See Appendix F for the list of qualifying immunosuppressive medications.

6 Medically stable defined as disease not requiring significant change in maintenance therapy or hospitalization for worsening disease or any recent CV event (eg, acute myocardial infarction, thromboembolic event) during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study

intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine or serum (β-hCG) pregnancy test result at screening and Visit 1 before the administration of study intervention.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of IV or SC immunoglobulin within 6 months prior to Visit 1 or expected to receive IV or SC immunoglobulin 6 months after dosing.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study (except where the participant ceased IMP treatment > 90 days and is in the follow-up period of the study and not expected to receive further IMP).

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156/AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

### 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5

Prior to receipt of the second dose of study intervention at Visit 5, participants should:

1 Have a negative rapid antigen test* for SARS-CoV-2.

2 Have a body weight ≥ 40 kg.

3 Have a negative serum or urine pregnancy test for WOCBP.

4 Not have received IV or SC immunoglobulin within 6 months prior to the second dose at Visit 5 or are expected to receive IV or SC immunoglobulin 6 months after dosing.

5 Not have received a COVID-19 vaccine within 14 days prior to the second dose at Visit 5.

6 Not have received COVID-19 antiviral for prophylaxis within 2 weeks prior to the second dose at Visit 5.

*If a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3).

Participants can wait up to 14 days to comply with criteria #5 or #6 above so as to be eligible for the second dose.

For instructions for participants who are not eligible for the second dose (Visit 5), see Section 7.1.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure or unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study, which can occur at any time during the enrollment period. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD3152 or placebo (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials.

AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD3152 in the Main Cohort, label-claim volume per vial is 2 mL.

AZD5156 (gluteal or thigh) is administered as 2 sequential IM injections, one injection for each component mAb, with the second injection administered in the contralateral side. AZD3152 will be administered as single IM injection (in the thigh). For AZD5156, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152.

Placebo will be supplied locally by the site. In the Sentinel Safety Cohort placebo will be administered as 2 IM injections, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). In the Main Cohort, placebo will be administered as a single IM injection in the thigh.

**Table 8 Investigational Medicinal Products**

| Intervention name | AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort [a] | AZD3152 for Main Cohort [a] | Placebo (Comparator) for Sentinel Safety and Main Cohorts |
|---|---|---|---|
| **Type** | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD3152 will be supplied as a single vial.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 300 mg AZD3152 at 150 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 300 mg single dose of AZD3152 | Single dose |
| **Vials required for constitution** | AZD1061; 2 vials<br>AZD3152; 1 vial | 1 vial | NA |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** [a] | **AZD3152 for Main Cohort** [a] | **Placebo (Comparator) for Sentinel Safety and Main Cohorts** |
|---|---|---|---|
| **Route of administration** [b] | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 1 IM injection (thigh) of 2 mL of AZD3152 | Sentinel Safety Cohort: 2 IM injections (gluteal or thigh); 3 mL and 2 mL<br>Main Cohort: 1 IM injection (thigh): 2 mL |
| **Use** | Investigational | Investigational | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] AZD3152 IMP will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive AZD5156 containing AZD3152 derived from cell pools material. In the Main Cohort, participants will receive AZD3152 derived from clonal cell material.

[b] The second injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The Investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156, AZD3152, and placebo for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (ie, the individual

storage time limits are not additive). AZD5156, AZD3152, and placebo do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD3152 or placebo (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and EVUSHELD use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD3152, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system

- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples (including the AstraZeneca Bioanalytical monitor)
- The unblinded Biometric teams (Statisticians and Programmers) both at AstraZeneca and its delegate and the DSMB

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy. SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5.1.2). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. All routine vaccines are permitted; however, they should not be given within 14 days before or after Visit 1 dosing of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 14 days before Visit 1 or during the study until at least after Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. The use of vitamins or occasional use of over-the-counter medications (eg, paracetamol, ibuprofen, antihistamines) would not exclude an individual from enrolling in the study.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | All routine vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments, and subsequently should not be given from 14 days prior to the second dose at Visit 5 until after the Day 210 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks prior each dose (Visit 1 or Visit 5) as well as during the study until after the Day 29 assessments following the first dose, and after the Day 210 assessments following the second dose of study intervention. If the participant develops COVID-19, standard of care treatment is allowed. |
| | Immunoglobulins (IVIG or SCIG) | Receipt of IV or SC immunoglobulin within 6 months prior to Visit 1 or expected to receive IV or SC immunoglobulin 6 months after each dose. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to the first dose of IMP and until 6 months after the last dose of IMP. |

IMP = investigational medicinal product; IVIG = intravenous immunoglobulins; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCIG = subcutaneous immunoglobulins.

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD3152 or placebo), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose.

If the participant experiences an immediate hypersensitivity reaction after their first dose of study intervention, the participant will be excluded from receiving a second dose of study intervention at Visit 5. If this occurs, the participant should remain in the study to be evaluated and complete all the remaining assessments as indicated in the SoA (Section 1.3). Also, if the participant is not eligible for the second dose (Visit 5), the participant should remain in the study to be evaluated and complete all the remaining assessments as indicated in the SoA. In the opinion of the Investigator or Sponsor, if any significant events should occur, this should be assessed and decided by the Investigator as to whether the participant should proceed in the study or be discontinued.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156. AstraZeneca will make the final decision after analysis of the safety data.

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any Grade 3 or higher AEs in 2 or more participants, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Main Cohort

The study will be put on temporary hold (defined as a pause in enrollment and/or dosing of participants into the Main Cohort) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In the event of a temporary hold for safety reasons, AstraZeneca will carefully review the totality of data and the risk to all participants will be evaluated thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing. If AstraZeneca determines that the study may be resumed, this may occur without a protocol amendment.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that, in the opinion of the Sponsor, may preclude further administration of IMP.
- If one or more participant experiences a grade IV hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If two or more participants, within the first 300 participants, experience a grade III or higher hypersensitivity reaction.
- If two or more participants, within the first 300 participants, experience a grade III or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with study intervention until the relevant safety review has been conducted.

If the study is suspended or the decision is made not to proceed to the Main Cohort, a protocol amendment will be submitted to Health Authorities.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 variants (Alpha, Omicron BA.2, Omicron BA.4/5, and Omicron XBB.1.5), using validated pseudovirus neutralization assays. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152.

### 8.1.2 Participant-reported COVID-19 Symptoms

For participants in the Main Cohort, to determine the incidence of infection, study sites will contact all participants weekly (prior to Day 361) and then monthly (from Day 361) (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (adapted from the WHO COVID-19 case definition WHO 2022) from the past week. An Unscheduled Visit should be conducted if a participant reports any COVID-19-like symptoms. At the Unscheduled Visit, the Investigator should discuss all symptoms the participant is experiencing including those that are mild to determine if the participant meets the clinical criteria adapted from the WHO COVID-19 case definition for an Illness Visit. If the participant meets the case definition, the COVID-19 initial assessment is started.

The Investigator site will need to conduct Illness Visits within 3 days of the qualifying symptoms being reported (see Section 8.1.3 for more on Illness Visits). Participants who develop any symptoms that could be due to COVID-19 must be advised to contact the study site as soon as possible.

Illness Visits should only be initiated if a participant meets either of the following criteria adapted from the WHO COVID-19 case definition clinical criteria (WHO 2022):

- Any two of the following: fever*, cough, positive COVID-19 test (rapid antigen test or RT-PCR)

OR

- Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever*, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia, conjunctivitis, positive COVID-19 test, symptom as judged by the Investigator to be related to COVID-19

*Subjective definition to be used for fever.

Participants who present with COVID-19 qualifying symptoms after Visit 1 in the Main Cohort will be instructed to attend the study site for Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever [≥ 38°C], cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020.

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site illness visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is

available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

At IL-D1, the study site will set up an illness e-Diary on the participant's own cellphone or equivalent device. If a participant does not have a suitable device the study site will issue an Illness e-Diary device. The study site will train the participant on how and when to complete the e-Diary and document their daily symptoms. Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in the Illness e-Diary. The status of ongoing symptoms reported in the e-Diary at the end of an illness series will be recorded. The end date for any symptoms still present after 14 days will be documented in the eCRF. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

For the duration of the Illness Visit period, sites should follow-up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants are to be encouraged to contact the site if their symptoms worsen.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required as detailed in the Laboratory Manual). Visit 5 (administration of the second dose of IMP) is only allowed to overlap with IL-D14. If Visit 5 is scheduled to occur at any of the other Illness Visit days, it should be delayed to IL-D14.

The Illness Visit assessment pathway may be initiated more than once (up to 10 times) for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories.

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of SARS-CoV-2 spike protein mutations identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs, and any observations will be documented in the participant's medical records (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as CV, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding from the time of study intervention administration should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again 10 to 15 minutes after the second injection is given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Electrocardiograms

A single 12-lead ECGs will be performed at screening for the Sentinel Safety Cohort and Main Cohort (time points specified in the SoA; see Section 1.3). A 12-lead ECG will be obtained after 5 minutes' supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal, borderline, or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as unscheduled assessments.

All ECG readings will be digitally stored as source documents.

### 8.2.4 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort (see Section 1.3.1, Section 1.3.2, and Section 1.3.3).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea (or blood urea nitrogen) | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T or I (Main Cohort; screening only) |
| Glucose (random) | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) (or international normalized ratio) |
| **Other (women of childbearing potential only)** | |
| Urine serum (β-hCG) pregnancy test | Follicle stimulating hormone [a] |

[a] For female participants aged < 50 years who are considered postmenopausal, will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.

β-hCG = beta human chorionic gonadotropin; ULN = upper limit of normal.

For female participants aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine or serum pregnancy test will be performed locally at screening (both cohorts), Visit 1 (both cohorts), and Visit 5 (Main Cohort only). For Visits 1 and 5, urine pregnancy test must be performed and be negative prior to dosing. This is especially important for any female participants who have not reached menarche at enrollment into the study and

whose child-bearing potential is expected to change during the study. A serum pregnancy test may be performed if a urine pregnancy test is not possible.

### 8.2.5 Other Safety Assessments

#### 8.2.5.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.5.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling may be recorded in the medical record at site visits.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after, 30 minutes (+ 10 minutes), and 1 hour after both injections are complete and also prior to participant release. Injection site reactions will also be monitored on Visit 2 (Day 3), Visit 3 (Day 5) and Visit 4 (Day 8) for the Sentinel Safety Cohort and Visit 2a (Day 8) and Visit 6 (Day 189) for the Main Cohort.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording

events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following each administration of study intervention. Adverse events occurring after 90 days following each study intervention administration and assessed by the Investigator as having a causal relationship to IMP and/or is COVID-19-related (eg, asymptomatic COVID-19) will be collected in the eCRF. Serious adverse events, MAAEs, and AESIs will be collected throughout the study.

Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156, AZD3152, and EVUSHELD in this study are based on those identified for EVUSHELD and are as follows:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events. These will be assessed by a CV Event Adjudication Committee (see Section 9.8)

### 8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoAs (Section 1.3).

Medically attended adverse events are defined as AEs leading to medically attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits (including Illness Visits themselves) will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the

study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active

follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156/AZD3152 and the active comparator product EVUSHELD are the respective Investigator's Brochures for the individual products.

### 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.10.1 Maternal Exposure

The IMP should not be given to pregnant women.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or**

**5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is

specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD3152, AZD5156, and AZD7442 in serum is a secondary

objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD3152 and (prior to CSP v7.0) AZD7442 from the Main Cohort, AZD5156 from the Sentinel Safety Cohort, and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156, AZD3152, and (prior to CSP v7.0) AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, serum samples will be collected and analyzed for the first 1200 participants (approximately). Serum samples will be collected for the rest of the participants for potential analysis as needed. Nasal lining fluid PK samples will be collected only for the first 600 participants (approximately). Samples from participants who receive placebo will be analyzed if required. Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max;}$
- $t_{max}$;

- $t_{½}$;
- $AUC_{last}$;
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD1061, AZD3152, and AZD8895 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated bioanalytical methods. For the Main Cohort, samples will be collected and analyzed for the first 1200 participants (approximately). Serum samples will be collected for the rest of the participants for potential analysis as needed. Samples from participants who receive placebo will be analyzed if required. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, including additional SARS-CoV-2 nAb, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative

RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD3152.

For storage, re-use and destruction of biomarker samples see Section 8.5.

#### 8.6.2.1 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing peripheral blood mononuclear cells using methods that may include flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor. Samples will be collected at Illness Visit time points specified in the SoAs (Section 1.3). Additionally, plasma may be isolated from the whole blood samples collected to isolate peripheral blood mononuclear cells, which can be utilized for exploratory immunogenicity and biomarker analyses.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants randomized to the comparator arm in the Main Cohort may have received doses of EVUSHELD or placebo at either first or second IMP administration and will be presented as a combined comparator study arm for the efficacy evaluation. Safety data will be summarized by each comparator group (EVUSHELD or placebo) separately and combined. When appropriate, actual dose(s) received may be presented separately to the combined comparator group. Any participant who received or was assigned to EVUSHELD at the first or second IMP dose will be presented as having received or been assigned to EVUSHELD. The SAP will provide details on the presentation of data by assigned and actual treatments received.

## 9.1 Statistical Hypotheses

The dual primary efficacy objectives are to:

- Compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant observed at any time up

to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations).

- Compare the efficacy of AZD3152 to EVUSHELD and/or placebo in the prevention of symptomatic COVID-19 attributable to matched variants observed at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations).

For each endpoint, a superiority test will be performed to compare the hazard rate of symptomatic COVID-19 between treatment arms. Two separate null hypothesis will be evaluated using the Holm step-down procedure to control the overall type I error across primary endpoints at 5% ($\alpha = 0.05$). A positive study will be declared if either dual primary endpoint is statistically significant. The hypotheses are as follows:

$$H_0: \quad \frac{\lambda_{\mathrm{AZD3152}}}{\lambda_{\mathrm{comparator}}} \geq 1.0,$$

$$H_A: \quad \frac{\lambda_{\mathrm{AZD3152}}}{\lambda_{\mathrm{comparator}}} < 1.0,$$

where $\lambda_{\mathrm{AZD3152}}$ and $\lambda_{\mathrm{comparator}}$ represent the instantaneous symptomatic COVID-19 hazard rates of AZD3152 and comparator arms, respectively, from all confirmed events or from a subset of events attributable to matched variants.

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the Parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD3152 or comparator.

The overall symptomatic COVID-19 blinded event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed.

The sample size in the Main Cohort was derived prior to the inclusion of the matched variant endpoint (introduced in CSP v8.0) and statistical testing of two primary efficacy endpoints. A

target sample of approximately 3200 participants was selected to reach the required number of events. Where approximately 40 events would provide at least 90% power to demonstrate that the lower bound of the 2-sided 95% CI is less than 1, under the assumption that the annual event rate will be approximately 3.2% in the comparator arm, HR of 0.30 (70% efficacy), significance level of $\alpha = 0.05$, and 10% attrition. Assumptions are based on data from prior studies with EVUSHELD and reported estimates of the event rate among those with immunocompromising conditions (Kelly et al 2022).

The addition of dual primary efficacy endpoints has not changed the study target enrollment. Assumptions for the dual efficacy endpoints, all confirmed events and events attributable to matched variants, are presented in Table 12 and Table 13 with varying levels of AZD3152 resistance. The efficacy of resistant variants such as those with the F456L mutation is assumed to be 0% and efficacy for matched variants at 70%. It is projected that if AZD3152-resistant events do not exceed 67% in the study, the efficacy for all confirmed events could be within the range of 30% to 60%, ensuring at least 90% power with the current enrolment target of N = 3200. For the matched variants endpoint, the endpoint with events attributed to matched variants requires at least 43 matched events to maintain 90% power. Significance level of $\alpha = 0.025$ has been used for both calculations.

The Main Cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD3152 compared with 1600 participants receiving comparator within the study.

**Table 12 Estimated Primary Events and Assumptions**

| | **Endpoint 1 All Confirmed Events** | **Endpoint 2 – Matched Variant Events** |
|---|---|---|
| Target enrolment | Approximately 3200 participants (Main Cohort) | |
| Type 1 error control | Holm's step-down procedure to maintain overall type I error across primary endpoints at 5% ($\alpha = 0.05$) | |
| Assumed efficacy | Symptomatic COVID-19 efficacy is assumed to range between 30% to 60% | Symptomatic COVID-19 attributable to matched variants efficacy assumed to be 70% |
| Target events | A minimum of 68 events are required to provide > 90% power under assumptions outlined in Table 13 | A minimum of 43 matched variant events are required to provide > 90% power (assumed efficacy 70%) |

**Table 13 Number of Events Required by Maximum Resistant Variant Proportions for Endpoint 1 – All Confirmed Events**

| **Assumed Efficacy (All confirmed events)** | **Maximum Proportion of AZD3152 Resistant** | **Events required for 90% Power** |
|---|---|---|
| 70% | 0% | 43 |

**Table 13 Number of Events Required by Maximum Resistant Variant Proportions for Endpoint 1 – All Confirmed Events**

| Assumed Efficacy (All confirmed events) | Maximum Proportion of AZD3152 Resistant | Events required for 90% Power |
|---|---|---|
| 60% | 20% | 68 |
| 50% | 38% | 112 |
| 40% | 54% | 199 |
| 30% | 67% | 398 |

## 9.3 Populations for Analyses

The following populations are defined:

**Table 14 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | These populations will consist of all randomized participants who received part or all of study intervention. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. Participants in the FAS will be classified according to the assigned treatment. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2-negative analysis set | This population will consist of all participants in the FAS without evidence of a current SARS-CoV-2 infection at baseline. Participants with a positive RT-PCR test results at baseline will be excluded. In the event multiple tests results are collected and in conflict, the last baseline central RT-PCR test will be used. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |

**Table 14 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Anti-drug antibody analysis set | All safety analysis set participants with a non-missing baseline and at least one non-missing post-baseline ADA result of the mAb component(s) evaluated. EVUSHELD and AZD5156 participants will be considered ADA-evaluable if either one or both of the respective mAb components includes a baseline and post-baseline result of the individual component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the indicated treatment classification in the corresponding analysis set population.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses. Methods for controlling multiplicity across endpoints will be presented in the Statistical Analysis Plan.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Confirmed Symptomatic COVID-19 Endpoint

The confirmed symptomatic COVID-19 efficacy endpoint is classified as a binary outcome and analyzed using survival methodology. The analysis incorporates the time in days from IMP administrations until a participant develops their first symptoms for COVID-19 at any time up to 181 days after last dose (ie, Visit 9 [Day 361] for participants who receive both planned treatment administrations). Positive cases require a central RT-PCR test and meet the qualifying symptoms as indicated by the Investigator satisfying the modified WHO definition

of symptomatic COVID-19 (see Section 8.1.2). The analysis will be based on the SARS-CoV-2-negative analysis set. The confirmed symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazards model, which includes study intervention and stratification factors as covariates to compare prophylactic efficacy (ie, 1-HR) of AZD3152 versus comparator. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including analyses using data after intercurrent events and a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Intercurrent events include participants who become unblinded to study intervention assignments and/or take other non-investigational product(s) for COVID-19 prevention prior to meeting the criteria for the COVID-19 endpoint. Such participants will be censored at the earliest of the following:

- The date of unblinding
- Receipt of the first dose of any COVID-19 preventive product

Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and will be included in the analysis. Participants who withdraw early from the study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

#### 9.4.2.2 Primary Matched Variant Endpoint

The analysis approach for the matched variant endpoint will follow a methodology similar to that of the confirmed Symptomatic COVID-19 endpoint. However, this endpoint will specifically include only symptomatic COVID-19 events attributable to SARS-CoV-2 variants susceptible to AZD3152 (ie, excluding variants with the F456L mutation). The same analysis population and Cox proportional hazards model approach will be applied.

Intercurrent events include participants who become unblinded to study intervention assignments and/or take other non-investigational products for COVID-19 prevention prior to meeting the criteria for the COVID-19 endpoint. Additionally, COVID-19 infections unrelated to matched or undetermined variants will be considered intercurrent events. Such participants will be censored at the earliest of the following:

- The date of unblinding
- Receipt of the first dose of any COVID-19 preventive product
- Date of first occurrence of an RT-PCR-confirmed symptomatic COVID-19 case not attributable to a matched variant

#### 9.4.2.3 Secondary Efficacy Endpoints

Efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is classified as a binary outcome. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point based on the SARS-CoV-2-negative analysis set.

- Incidence of post treatment confirmed symptomatic COVID-19 attributable to any SARS-CoV-2 variant
- Incidence of post treatment symptomatic COVID-19 attributable to a matched variant
- Incidence of severe COVID-19 attributable to any SARS-CoV-2 variant
- Incidence of severe COVID-19 attributable to a matched variant
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by SARS-CoV-2 variant, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers with SARS-CoV-2 variants, including Alpha, Omicron BA.2, Omicron BA.4/5 and Omicron XBB.1.5 between treatment groups will be conducted using GMT ratio. Additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152. Analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

### 9.4.4 Anti-drug Antibody Variables

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed. Further details are provided in the SAP.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, where possible, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Pharmacokinetic parameters will be estimated for AZD3152 and AZD1061 separately and for the combination of the 2 component mAbs of AZD5156. The following single dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$. AZD5156, AZD3152, and AZD1061 serum concentrations will also be summarized using descriptive statistics in the Sentinel Safety Cohort.

Following initial dosing with AZD3152 or EVUSHELD, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

## 9.5 Planned Analyses

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants complete Visit 6 (Day 29), Visit 8 (Day 91), Visit 9 (Day 181), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK concentrations at Day 29. The remaining two analyses will include all available data when conducted.

The study will maintain a double-blind period until a median follow-up time is greater than 181 days in the SARS-CoV-2-Negative Set and the required number of events are observed for the dual primary endpoints to support the primary efficacy and safety objectives and trigger the primary analysis. The exact number of events required for the primary analysis will be based on the prevalence of resistant events (variants with F456L mutation) within the study and will be documented in the SAP. If it is unlikely that sufficient events will be observed for either endpoint or all participants have been followed for more than 361 days or withdrawn from the study, the database will be locked for primary analysis.

To maintain the integrity of the study for rigorous evaluation of safety and efficacy through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analyses will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan. Participant-level unblinding information will be kept strictly

confidential, and the rationale for any unblinding will be documented. An additional interim analysis may be conducted to evaluate efficacy of the first IMP dose through Day 181, safety and PK of the second dose at Visit 7 (Day 210). This analysis will only be conducted if the primary analysis has been previously conducted and all participants have been followed for more than 181 days or withdrawn from the study. The SAP will describe the planned analyses in greater detail.

If there is a medical need for AZD3152 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis and data readouts that may reveal treatment assignments if conducted prior to the primary analysis.

## 9.6 Safety Review Committee – Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Sentinel Safety Cohort, as discussed in Section 4.1.1.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD3152) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB

will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

## 9.8 Cardiovascular Event Adjudication Committee

For the Main Cohort only, an independent CV Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of blinded data to systematically evaluate CV events. The adjudicated CV events will be included in descriptive analyses of safety data. Further details of the CV Event Adjudication Committee composition, operation, and listings of preferred terms to identify events are provided in a separate CV Event Adjudication Committee Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and Investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but

are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

# C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

(a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

(b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 15, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care.

# Appendix F List of Immunosuppressive Medications

The list of immunosuppressive medications in the table below is not exhaustive.

| **1. Alkylating Agents** | | | |
|---|---|---|---|
| Bendamustine | | Melphalan | |
| Busulfan | | Mitomycin | |
| Carboplatin | | Oxaliplatin | |
| Carmustine | | Procarbazine | |
| Cisplatin | | Streptozocin | |
| Cyclophosphamide | | Temozolomide | |
| Dacarbazine | | Thiotepa | |
| Ifosfamide | | Trabectedin | |
| Lomustine | | | |
| **2. Selective Immunosuppressants** | | | |
| General | | Calcineurin Inhibitors | Antimetabolites |
| Azathioprine | Lenalidomide | Cyclosporine | Methotrexate |
| Belumosudil | Mycophenolate | Tacrolimus | Nelarabine |
| Bortezomib | Pomalidomide | Voclosporin | Pemetrexed |
| Cladribine | Teriflunomide | | Pralatrexate |
| Dimethyl fumarate | Thalidomide | | Irinotecan |
| Diroximal fumarate | Anti-thymocyte immunoglobulin (horse, rabbit) | | Liposome |
| Leflunomide | | | Capecitabine |
| | | | Clofarabine |
| | | | Cytarabine |
| | | | Decitabine |
| | | | Floxuridine |
| | | | Fludarabine |
| | | | Fluorouracil |
| | | | Gemcitabine |
| | | | Mercaptopurine |
| JAK Inhibitors | | mTOR Inhibitors | Sphingosine-1-phosphate Receptor Modulators |
| Baricitinib | | Everolimus | Fingolimod |
| Tofacitinib | | Sirolimus | Ozanimod |
| Upadacitinib | | | Ponesimod |
| Peficitinib | | | Siponimod |
| Itacitinib | | | |
| **3. Monoclonal Antibodies** | | | |
| General | | Anti-IFN | Anti-CD20 |
| Alemtuzumab (anti-CD52) | | Anifrolumab | Ibritumomab |
| Belimumab | | Emapalumab | Obinutuzumab |
| Begelomab (anti DPP-4/CD26) | | | Rituximab |
| Teprotumumab (anti-IGF-1) | | | Ocrelizumab |
| Inebilizumab (anti-CD19) | | | Ofatumumab |
| Muromonab (anti-CD3) | | | |
| Inotuzumab Ozogamicin (anti-CD22) | | | |

| Selective T-Cell Costimulation Blockers | Integrin Receptor Agonists | Bruton Tyrosine Kinase Inhibitors | |
|---|---|---|---|
| Abatacept<br>Belatacept | Natalizumab<br>Vedolizumab | Ibrutinib<br>Acalabrutinib<br>Pirtobrutinib | Zanubrutinib<br>Deucravacitinib |
| Complement Inhibitors | TNF-alpha Inhibitors | IL-23 Inhibitors | |
| Pegcetacoplan<br>Eculizumab (anti-C5)<br>Ravulizumab (anti-C5)<br>Sutimlimab (anti-C1) | Adalimumab<br>Afelimomab<br>Certolizumab Pegol<br>Etanercept<br>Golimumab<br>Infliximab | Ustekinumab<br>Guselkumab<br>Tildrakizumab<br>Risankizumab | |
| IL-17 Inhibitors | IL-1 Inhibitors | IL Inhibitors (other) | |
| Secukinumab<br>Ixekizumab<br>Bimekizumab<br>Brodalumab<br>Netakimab | Anakinra<br>Canakinumab<br>Rilonacept | Basilximab (anti IL-2)<br>Sarilumab (anti IL-6)<br>Satralizumab (anti IL-6)<br>Siltuximab (anti IL-6)<br>Tocilizumab (anti IL-6)<br>Spesolimab (anti IL-36) | |
| **4. Steroids** | | | |
| Dexamethasone: ≥ 3 mg per day, minimum of 2 weeks of therapy<br>Prednisolone: ≥ 20 mg per day, minimum of 2 weeks of therapy<br>Prednisone: ≥ 20 mg per day, minimum of 2 weeks of therapy | | | |

CD = cluster of differentiation; DPP = dipeptidyl peptidase; IFN = interferon; IFG = insulin-like growth factor; IL = interleukin; TNF = tumor necrosis factor.

# Appendix G Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 7.0 [14 June 2023]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

### Overall Rationale for the Modification:

The protocol has been amended primarily to change the comparator for the Main Cohort from (active) EVUSHELD to placebo. This change was initiated as the Parent study is now primarily an efficacy and safety study.

A summary of changes is presented below. Where applicable, the changes were also applied to the synopsis.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global change | For the Main Cohort, the comparator has been changed from (active) EVUSHELD to placebo. As placebo comparator will be given as a single injection (whereas EVUSHELD required two injections) at each dosing occasion, the injection of matching placebo that was part of the blinded AZD3152 administration has been removed | Change made in response to Health Authority feedback |
| Global change | "AZD7442" has been changed to "EVUSHELD" throughout except in places where AZD7442 would be more appropriate (eg, PK) | Clarification of the name for the comparator |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.5.1.1 Determination of Drug Concentration<br>8.5.2.1 Anti-drug Antibody Assessments | Serum PK and ADA/nAb samples will now be collected and analyzed only for the first 1200 participants (approximately) in the Main Cohort, although serum samples will still be collected from all participants for potential future analyses | It is anticipated that data from 1200 participants should be sufficient for the purposes of these analyses, but serum samples will also be collected from the other participants for potential future analyses. |
| 2.1 Study Rationale<br>4.1 Overall Design | Added justification for change of comparator to placebo, and also describe the three possible combinations of comparator that a Main Cohort Participant could receive | Justification required due to the change of comparator |
| 4.2.3 Rationale for Use of Placebo as Comparator for the Main Cohort | Section has been reconfigured to show rationale for use of placebo as comparator (not AZD7442) | Update because of change of comparator |

| | | |
|---|---|---|
| 5.2.1 Inclusion Criteria | Updated Inclusion criterion #5 to include advanced or untreated HIV infection (people with HIV and history of CD4 cell counts < 200/$mm^3$ within 6 months of Visit 1, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) | Immunobridging endpoint was removed and the SARS-CoV-2 nAb analysis is now a descriptive analysis; therefore, there is flexibility to include advanced and untreated HIV participants (for some of which we may not be able to determine the SARS-CoV-2 nAb titers in the lentivirus based pseudovirus assay) to the immunocompromised population |
| 5.2.2 Exclusion Criteria | Removed (previous) Exclusion criterion #7 (Has HIV infection) | Immunobridging endpoint was removed and the SARS-CoV-2 nAb analysis is now a descriptive analysis; therefore, there is flexibility to include advanced and untreated HIV participants (for some of which we may not be able to determine the SARS-CoV-2 nAb titers in the lentivirus based pseudovirus assay) to the immunocompromised population |
| 8.5.1.1 Determination of Drug Concentration | Serum PK samples will now be collected and analyzed only for the first 1200 participants (approximately) in the Main Cohort, although serum samples will still be collected from all participants for potential future analyses. Samples from participants who receive placebo will be analyzed if required. | It is anticipated that data from 1200 participants should be sufficient for the purposes of these analyses, but serum samples will also be collected from the other participants for potential future analyses. |
| 8.5.2.1 Anti-drug Antibody Assessments | Samples for determination of ADA will now be collected and analyzed only for the first 1200 participants (approximately) in the Main Cohort, although serum samples will still be collected from all participants for potential future analyses. Samples from participants who receive placebo will be analyzed if required. | It is anticipated that data from 1200 participants should be sufficient for the purposes of these analyses, but serum samples will also be collected from the other participants for potential future analyses. |
| 9 STATISTICAL CONSIDERATIONS | Added details of the combined comparator study arm for the efficacy evaluation | Some participants in the Main Cohort will have received EVUSHELD (prior to CSP v7.0) as comparator while others (as of CSP v7.0) will receive placebo |

| | | |
|---|---|---|
| 9.5 Planned Analyses | Noted that primary analysis will only be conducted once median follow-up time is greater than 181 days in the full analysis set | Clarified the timing of the analysis |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global change | When discussing the present study, the word 'control' has been substituted with 'comparator' | More appropriate language is now used considering the switch from AZD7442 to placebo as comparator |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.2.4 Clinical Safety Laboratory Assessments | Minor change to language: pregnancy tests will be done locally (not specifically at a local laboratory) | Clarification, as tests may be performed at the clinic |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added footnote to allow the screening troponin test to be performed on Day 1 (predose) and noted in the table that this assessment will be done using a local laboratory | Reflection of clinical practice |
| 2.1 Study Rationale<br>4.1 Overall Design | Noted that the sub-study will be Phase II | Clarification |
| 2.1 Study Rationale | Noted that the sub-study will be described in an addendum. | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |
| 2.2.2 AZD5156, AZD3152, and EVUSHELD | Removed reference to "the ongoing pandemic" | Updated to reflect the decline in COVID-19 incidence |
| 3 OBJECTIVES AND ENDPOINTS | Clarified time of adverse event assessments | Clarification |
| 4.3 Justification for Dose | Removed sub-section "Justification for AZD7442 Dose" | Comparator is now placebo for the Main Cohort |
| 5.2.1 Inclusion Criteria | For inclusion criterion #5, the bullet point regarding moderate or severe primary or secondary immunodeficiency has been reworded. | Reworded for clarity/readability |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5 | Noted that requirement for negative pregnancy test was only for WOCBP, that participants can wait up to 14 days to comply with criteria #5 or #6, and that instructions for participants who are not eligible for the second dose (Visit 5) are in Section 7.1. | Clarifications |
| 6.5 Concomitant Therapy | In the table, the timeline for COVID-19 antivirals has been reworded for clarity | Clarification |
| 8.2.1 Physical Examinations | Each clinically significant abnormal finding from the time of study intervention administration (was previously following randomization) should be reported as an AE | Timeframe updated for consistency with AE collection period noted in Section 8.3.1 |
| 9.4.5 Safety | Noted that the most recent version of MedDRA will only be used where possible | Contingency, as it may not always be possible to use the latest version |

**CSP Version 6.0 [24 May 2023]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended primarily to add a sub-study as an Addendum to the Parent study, to upgrade efficacy to a primary endpoint, and to provide additional clarification of the study design elements that impact the recruitment of the Main Cohort.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page<br>Synopsis<br>2.1 Study Rationale<br>3 Objectives and Endpoints<br>4.1 Overall Design<br>4.2 Scientific Rationale for Study Design<br>9 Statistical Considerations | Efficacy has been upgraded to a primary endpoint<br><br>nAb responses to the SARS-CoV-2 Alpha variant is no longer a primary endpoint for the Main Cohort | To allow the collection of efficacy data to support a 300 mg dose<br><br>In accordance with regulatory guidance, the immunobridging objective will be explored through the sub-study |
| Synopsis<br>2.1 Study Rationale<br>4.1 Overall Design | Added text to introduce the inclusion of a separate SUPERNOVA sub-study as an Addendum | Based on FDA feedback, a sub-study has been added to be conducted in the US only |
| Synopsis<br>3 Objectives and Endpoints | Added AZD5156, AZD3152, and AZD1061, ADA titers to the incidence of ADA endpoint for the secondary objective of ADA response evaluation for the Sentinel Safety Cohort | For clarification. |
| Synopsis<br>3 Objectives and Endpoints<br>8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments<br>9 Statistical Considerations | Revised the secondary endpoint for the Main Cohort for the comparison of the nAb responses to the SARS-CoV-2 variants. The text has been updated to specify Alpha, Omicron BA.2, Omicron BA.4/5 and/or Omicron XBB.1.5 in serum following AZD3152 and AZD7442 administration | To add additional SARS-CoV-2 variants as the primary nAb endpoint with nAb responses to the SARS-CoV-2 Alpha variant was removed |
| Synopsis<br>3 Objectives and Endpoints<br>8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments<br>9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Added text to reflect that additional SARS-CoV-2 variants may also be assessed to support study activities and the evaluation of AZD3152 | Additional text was added to ensure additional SARS-CoV-2 variants will be assessed |
| Synopsis<br>3 Objectives and Endpoints | Added AZD3152, AZD7442, AZD1061, and AZD8895, ADA titers to the incidence of ADA endpoint for the secondary objective of ADA response evaluation for the Main Cohort | For clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>4.1 Overall Design<br>4.1.1 Sentinel Safety Cohort<br>9.2 Sample Size Determination | Added "approximately" to "56 healthy adults" | To allow for any small number of additional participants in the Sentinel Safety Cohort |
| Synopsis<br>9 Statistical Considerations | Section has been updated | Changes added to align with the upgrading of efficacy to a primary endpoint and the removal of the primary endpoint of nAb responses to the SARS-CoV-2 Alpha variant |
| 1.3 Schedule of Activities<br>1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Updated the screening period for the Main Cohort participants to "up to 14 days (Day -14 through Day 1)" | To facilitate the collection of medical history information |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Removed the assessment of eligibility criteria verification from Visit 5, and added a new row to verify selected eligibility criteria for receipt of second dose (Visit 5) with footnote [c] to see Section 5.2.3 | To clarify the eligibility criteria for receipt of second dose of study intervention |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added a new footnote [d] to the full physical examination assessment during the Early Discontinuation Visit to exclude height measurement in adults aged 18 years and older during the assessment | For clarification. |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>5.2.2 Exclusion Criteria (Main Cohort)<br>8.2.4 Clinical Safety Laboratory Assessments | Updated the pregnancy testing to reflect that a serum pregnancy test may be substituted for a urine pregnancy test where a urine pregnancy testing is unavailable | This change has been made to allow for pregnancy testing in female participants who are unable to produce urine |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added a new footnote [h] to the rapid antigen test for SARS-CoV-2 (performed locally) assessment at Visit 5 to note that if a participant has a positive rapid antigen test and is asymptomatic, then the dose should be held and the participant should be re-tested at 7 days (+ 3 days), and if the repeat test is negative, the participant can be dosed. If a participant has a positive | To provide flexibility regarding the second dose administration of IMP in participants who have a positive rapid antigen test at Visit 5 and aligned to Section 8.1.3 on Illness Visits. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | rapid antigen test and is symptomatic, then the participant should follow the process outlined for Illness Visits (see Section 8.1.3) | |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.1.2 Participant-reported COVID-19 Symptoms | Added a new row for assessments of "Monthly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms", adjusted footnote [l] (previous footnote [i]) for clarification | Telephone contact will take place weekly prior to Day 361, and monthly from Day 361 to reduce the site and participant burden |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>4.1 Overall Design<br>8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Added footnote [m] and updated text in Sections 4.1 and 8.3.1 to clarify that AEs occurring after 90 days following each study intervention administration and assessed by the Investigator as having a causal relationship to IMP and/or COVID-19-related but does not prompt and Illness Visit (eg, asymptomatic COVID-19) will be collected on the AE CRF page | This change has been made in case events occur outside of the AE windows (after 90 days following each study intervention) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants<br>8.5.1.1 Determination of Drug Concentration<br>8.5.2.1 Anti-drug Antibody Assessments | Removed footnote [o] (previous footnote [k]) from assessments of PK serum sample and ADA and antidrug nAbs assessment serum sample and accordingly updated the text in Sections 8.5.1.1 and 8.5.2.1 to clarify that nasal lining fluid PK samples will only be collected for the first 600 participants (previously 1200 participants) | To extend the analysis of PK, ADA, and antidrug nAbs to the full enrolled population<br>Reduced the number of nasal lining fluid samples to 600 as the previous number of 1200 was aligned to the immunobridging endpoint, which has now been removed from this protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added "and 1 hour" to footnote [p] | This change has been made to allow evaluation of safety and tolerability 1 hour after both injections are given and also aligned to Section 8.2.5.2 on Immediate Adverse Events which are assessed 1 hour after both injections |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added a column for the Unscheduled Visit to verify qualifying symptoms with footnote [d] to clarify that if the participant meets the clinical criteria adapted from WHO COVID-19 case definition, then an illness visit (IL-D1) will be initiated | Added a column to clarify the requirements for the Unscheduled Visit and for which an Illness Visit series should be initiated |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Updated the window for Visit IL-D14 to + 2 days | The participant e-Diary will need to be completed up to and including IL-D14 |
| | Updated footnote [e] to reflect that central RT-PCR laboratory test results may not be reported to sites during the Illness Visit period | For clarification |
| | Telephone contact for safety monitoring has been added to the visits IL-D5 and IL-D11 and footnote [f] has been added to note that for the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen | This change has been added to ensure telephone contact is made with the participant on each home Illness Visit |
| | Added “WHO Clinical Progression Scale” assessments to the Illness Visits with footnote [f] for clarification | To clarify that the WHO Clinical Progression Scale score is required for each site Illness Visit |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Changed “Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic” to “Coronavirus SARS-CoV-2 is the causative agent of COVID-19” | Updated to the current WHO status for COVID-19 |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Changed “against the more recent Omicron variants BA.2, BA.3, and BA.4/5” to “against some of the | To add clarity since additional variants have emerged |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | more recent Omicron variants such as BA.2, BA.3, and BA.4/5" | |
| 3 Objectives and Endpoints | Added an exploratory objective to characterize the predicted serum nAb responses to SARS-CoV-2 variants following IMP administration. The endpoint will be descriptive statistics for predicted GMTs will include the number of participants, geometric mean, gSD, 95% CI, summarized by treatment arm and visit for select SARS CoV-2 variants using PK and in-vitro $IC_{50}$ values | To align with the removal of the primary immunobridging endpoint, this exploratory objective has been added to characterise nAb titers associated with each treatment arm |
| 4.1 Overall Design<br>6.5 Concomitant Therapy | Updated text to reflect that SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments, and subsequently should not be given from 14 days prior to the second dose at Visit 5 and until after the Day 210 assessments | The timing of the restriction was re-aligned from Day 29 to the assessments that occur at Visit 3 which may occur up to 3 days post Day 29, as per the 3-day visit window. Restrictions of SARS-CoV-2 vaccines added to the second dose, were included to prevent confusion around possible reactogenicity of the vaccine at the time of the second dose being administered |
| 4.1 Overall Design<br>8.1.2 Participant-reported COVID-19 Symptoms | Updated text to reflect that the clinical criteria for SARS-CoV-2 infection in the protocol is adapted from the WHO COVID-19 case definition and a reference to the most recent WHO COVID-19 case definition (July 2022) has been added | Clinical criteria for SARS CoV-2 infection in this protocol have been adapted from the WHO COVID-19 case definition |
| 5.2.1 Inclusion Criteria (Main Cohort) | Updated Inclusion criterion #3 to reflect that participants should have a negative rapid antigen test prior to dosing at Visit 1 and removed "Visit 5" | This change has been made to note that a negative rapid antigen test must be obtained prior to the first dose of study intervention to confirm eligibility for entry into the study. Visit 5 was removed from the entry criteria given that the participant is already entered into the study, and instead eligibility for the second dose of study intervention will be verified at Visit 5 |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Updated Inclusion criterion #4 to reflect that participants weights should be ≥ 40 kg at screening and removed "Visit 5" | To ensure that the participant has a safe weight for receiving study intervention to confirm eligibility for entry into the study. Visit 5 was removed from the entry criteria given that the participant is already entered into the study, and instead eligibility for the second dose of study intervention will be verified at Visit 5 |
| | For Inclusion criterion #5, changed "active treatment" to "active immunosuppressive treatment" (first bullet), and removed the examples | To clarify the active treatment must be immunosuppressive. The examples were excluded as they would not meet the new definition |
| | Updated the inclusion criteria of participants who previously had a transplant (third bullet) | To clarify the inclusion of participants who previously had a transplant |
| | Changed "other immunosuppressive or immunomodulatory biologic agents" to "other immunosuppressive biologic agents" (fourth bullet) | To ensure that the entry criteria include those participants who are on medication that leave them immunosuppressed |
| | Removed "Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia" (seventh bullet) | Text removed to be consistent with Exclusion criterion #8 regarding the use of IVIG and SCIG |
| | For Inclusion criterion #6, changed "change in therapy" to "change in maintenance therapy" and added "or any recent cardiovascular event (eg, acute myocardial infarction, thromboembolic event)" | Added language around therapy for clarification, and additional language including cardiovascular events to ensure participant is medically stable prior to study entry |
| 5.2.2 Exclusion Criteria (Main Cohort) | Updated Exclusion criterion #1 to include a negative serum pregnancy and that a negative urine or serum pregnancy test must be obtained prior to Visit 1 | This change was made because a urine pregnancy test is not possible in all female participants and to note that a negative pregnancy test should be obtained prior to both the first and second dose of study intervention |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Added Exclusion criterion #8, to state that participants being treated with intravenous or subcutaneous immunoglobulins (IVIG or SCIG) within 6 months prior to Visit 1 or are expected to receive IVIG or SCIG within 6 months after dosing should be excluded from the study | IVIG/SCIG treatment may confound the neutralizing antibody results |
| 5.2.3 Eligibility Criteria for Receipt of Second Dose at Visit 5 | New section | This section has been added to clarify the eligibility criteria prior to receipt of the second dose of study intervention at Visit 5 |
| 5.4 Screen Failures | Updated the text to remove the 2-week window in which the single rescreening could occur and added text to specify that the rescreening can occur at any time during the enrollment period | Removed the 2-week window to reflect the immunocompromised population |
| 6.1 Study Intervention(s) Administered | Updated Table 8 to indicate how many vials are required to constitute AZD1061, AZ8895, and AZ3152 | For clarification |
| 6.5 Concomitant Therapy | Updated Table 9 to reflect that participants must not have COVID-19 antivirals for prophylaxis 2 weeks prior to Visit 1, and during the study until after the Day 29 assessments following the first dose, and after the Day 210 assessments following the second dose of study intervention | This change was made to note that the restrictions for COVID-19 antivirals applies to both the first and second dose of study intervention, so as to avoid confounding the results of the immune sampling. The timing of the restriction was re-aligned from Day 29 and Day 210 to the assessments that occur at Visit 3 and Visit 7 which may occur up to 3 days post Day 29 and Day 210 respectively, as per the 3-day visit window |
| | Updated Table 9 to include intravenous or subcutaneous immunoglobulins (IVIG or SCIG) in “restricted” | IVIG/SCIG treatment may confound the study results and therefore, has been excluded from the study |
| | Updated Table 9 to reflect EVUSHELD should not be given within 6 months prior to each dose of IMP and until 6 months after the last dose of IMP | EVUSHELD treatment may confound the study results and therefore the criteria around the timing have been clarified |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.1 Discontinuation of Study Intervention | Updated the text to reflect that if the participant experiences an immediate hypersensitivity reaction after either IM injection, the participant will be excluded from receiving a second dose of study intervention at Visit 5 and that the participant will continue in the study and complete all scheduled assessments and sampling to end of the study | Clarification around receiving the second dose following hypersensitivity reactions |
| | Updated the text to reflect that participants who miss or are not eligible to receive the second dose of study intervention will continue in the study and complete all scheduled assessments and sampling to end of the study | For clarification |
| 7.2.2 Stopping Rules for Main Cohort | New section | Section 7.2.2 has been added to specify stopping rules for the Main Cohort |
| 8.1.2 Participant-reported COVID-19 Symptoms | Updated text to clarify the participants for which an Unscheduled Visit should be conducted and for which an Illness Visit series should be initiated | Clarified the participants for which an Unscheduled Visit should be conducted and for which an Illness Visit series should be initiated |
| | Updated the clinical criteria for SARS-CoV-2 infection based on those adapted from the WHO COVID-19 case definition | Clinical criteria for SARS-CoV-2 infection in this protocol have been adapted from the WHO COVID-19 case definition to account for a positive COVID-19 test performed off-site and any potential new symptoms that could develop given the rapidly changing landscape of COVID-19 variants |
| | Clarified that fever is subjective for the clinical criteria adapted from WHO COVID-19 case definition | Updated to clarify that a subjective assessment of fever will be utilized |
| | Added text to define fever for severe COVID -19 at ≥ 38°C. | For clarification. |
| 8.1.3 Illness Visits | Text added to reflect that the study site will set up an illness e-Diary on the participant's own device (if available) as the primary approach | For clarification. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Text added to reflect that for the duration of the Illness Visit period, sites should follow up with the participant to determine if there has been a change to their symptoms that may indicate worsening of symptoms that meet SAE, MAAE or AESI criteria and worsening of their WHO progression score. Participants to be encouraged to contact the site if their symptoms worsen | Clarification provided to ensure study sites follow-up with the participants for symptoms and safety information |
| | Text added to state that Visit 5 (administration of the second dose of IMP) is only allowed to overlap with IL-D14. If Visit 5 is scheduled to occur at any of the other Illness Visit days, it should be delayed to IL-D14. | To prevent IMP dosing during an Illness Visit assessment pathway. |
| 8.2.3 Electrocardiograms | Added text to clarify that a single 12-lead ECG will be performed at screening for the Sentinel Safety Cohort and Main Cohort | For clarification |
| | Changed “normal or abnormal” to “normal, borderline, or abnormal” | For clarification |
| 8.2.5.2 Injection Site Reactions | Added text to state that injection site monitoring will also be performed at 1 hour after both injections for the study intervention dose are given, and that injection site reactions will be monitored on Visit 2 (Day 3), Visit 3 (Day 5) and Visit 4 (Day 8) for the Sentinel Study and Visit 2a (Day 8) and Visit 6 (Day 189) for the Main Study | This change has been made to align with Section 8.2.5.2 on Immediate Adverse Events which are assessed 1 hour after both injections |
| 8.3.2 Follow-up of AEs and SAEs | Removed “maximum severity grade” from adverse event variables | Maximum severity grade will be derived and therefore is not required to be collected from the CRF |
| 8.3.5 Medically Attended Adverse Events | Added text to clarify that Illness Visits themselves will not be considered as MAAEs | Clinic visits for scheduled procedures are not considered MAAEs |
| 8.3.10.1 Maternal Exposure | Added text to state that the IMP should not be given to pregnant women | For clarification of safety requirements |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.5.2.1 Anti-drug Antibody Assessments | Updated ADA to AZD1061, AZD3152, and AZD8895 will be determined (removed AZD5156 and AZD7442) | To clarify individual monoclonal antibodies to be evaluated. |
| Appendix F List of Immunosuppressive Medications | Added a new Appendix | To clarify which medications taken by participants will qualify them as immunocompromised |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms<br>4.1 Overall Design<br>8.1.3 Illness Visits | Updated text to clarify that duplicate sampling is not required where Main and Illness Visits overlap and added a reference to the Laboratory Manual | For clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | Changed “some markets” to “some regions”<br>Changed “at least some protection against SARS-CoV-2” to “at least some potential protection against SARS-CoV-2” | For clarification |
| 6.5 Concomitant Therapy | Changed “All other vaccines” to “All routine vaccines” | For consistency with Table 9 |
| 8.1.3 Illness Visits | Changed “site visits” to “site illness visits”<br>Added “up to 10 times” for Illness Visit initiations | For clarification<br>For clarification |
| 8.2.2 Vital Signs | Changed “after both injections” to “after the second injection” | This change has been made to clarify that vital signs will be monitored at 10 to 15 minutes after the second injection of the dose of study intervention is given |
| 8.2.3 Electrocardiograms | Added text to clarify that a single 12-lead ECG will be performed at screening for the Sentinel Safety Cohort and Main Cohort | For clarification |

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This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The initial development plan for AZD5156 focused on a combination of two mAbs (AZD1061 [cilgavimab] and AZD3152); however, after evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 alone, AstraZeneca has decided to pursue AZD3152 as a standalone therapy rather than in combination with AZD1061. Consequently, the Main Cohort of SUPERNOVA will now evaluate AZD3152 instead of AZD5156. The conduct of the Sentinel Cohort is unchanged and will be conducted with AZD5156.

Given that AZD3152 is a component of AZD5156, the safety for this mAb will be assessed in the Sentinel Safety Cohort prior to initiation of the Main Cohort. AstraZeneca does not expect any difference in safety profile between AZD3152 administered in combination with AZD1061 or administered alone, therefore the safety data on the combination as determined in the Sentinel Safety Cohort will be applicable to AZD3152 administered alone.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| TITLE PAGE | The study intervention has been changed from 'AZD5156' to 'AZD5156/AZD3152' and a similar change has been made to the study title | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy, although AZD5156 will still be studied in the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of follicle stimulating hormone at screening | Required for eligibility criteria |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples have been removed from Day 271 and the EDV | Rationalization of blood sampling to reduce invasive procedures |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Serum PK and ADA/nAb samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 2.1 Study Rationale | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.2.2 AZD5156, AZD3152, and AZD7442 | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 2.3 Benefit/Risk Assessment | Section updated throughout to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and overall benefit/risk conclusion aligned with Investigator's Brochure. | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy; also, text aligned with Investigator's Brochure |
| 3 OBJECTIVES AND ENDPOINTS | Created separate primary and secondary objectives and endpoints for the Sentinel Safety and Main Cohorts | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.1 Overall Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.2 Main Cohort | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156, and that an administration of placebo will be included with AZD3152 to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2 Scientific Rationale for Study Design | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.3 Rationale for Use of AZD7442 as Control for the Main Cohort | New section | Justification as to why AZD7442 is considered a better choice of control than placebo |
| 4.3.2 Justification for AZD3152 Dose | New section | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #10, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.1.2 Exclusion Criteria (Sentinel Safety Cohort) | For exclusion #21, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, any alkylating agents will qualify as a risk factor, not just high-dose agents | Low-dose cyclophosphamide is used as immunotherapy in lymphoma, breast and ovarian cancer |
| 5.2.1 Inclusion Criteria (Main Cohort) | For exclusion #5, a moderate or severe secondary immunodeficiency will now qualify as a risk factor | To broaden the study population |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #11, noted that COVID-19 antiviral would be for prophylaxis | Clarification |
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #13, noted that concurrent participation in another interventional study where the participant ceased IMP treatment > 90 days who is in the follow-up period of the study and not expected to receive further IMP is permitted for inclusion | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.2 Exclusion Criteria (Main Cohort) | For exclusion #17, changed 'AZD5156 program' to 'AZD5156/AZD3152 program' | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.1 Study Intervention(s) Administered | The whole section (including the table) has been updated to reflect the use of AZD3152 as a standalone therapy in the Main Cohort, including use of placebo to maintain the blind | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.5 Concomitant Therapy | Added more details regarding permitted concomitant medications for the Sentinel Safety Cohort and clarified the wording around SARS-CoV-2 vaccines and COVID-19 antivirals | Clarification |
| 8.5.1.1 Determination of Drug Concentration | Serum PK samples will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 8.5.2.1 Anti-drug Antibody Assessments | Samples for determination of ADA will now be collected only for the first 1200 participants (approximately) in the Main Cohort | Rationalization of blood sampling to reduce invasive procedures |
| 9.1 Statistical Hypotheses | The whole section has been updated to reflect the use of AZD3152 as a standalone therapy | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.2 Sample Size Determination | Section updated to reflect that study intervention for Main Cohort will be AZD3152 instead of AZD5156; minor adjustments made to wording of sample size determination | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Schema updated in line with applicable changes from the protocol text | Schema made consistent with amended text |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Timing of Day 1 urine pregnancy test changed from 'prior to randomization' to 'predose' and footnote updated to clarify test must be on same day as dosing | Consistency with other parts of the table |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Clarified that laboratory safety samples on Day 1 will be taken predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed from the table footnote) | Clarification regarding the time around vital signs collection |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Noted that duration of recording daily symptoms associated with COVID-19 will be 14 days | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | Updated statistics for COVID-19 cases | Information brought up to date |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | Statement is now less ambiguous |
| 4.1 Overall Design | Wording regarding qualification for Illness Visits has been updated | Clarification |
| 4.1.1 Sentinel Safety Cohort | Added justification for use of AZD5156 safety data to initiate dosing with AZD3152 in the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.2.1 Rationale for Administration Site | Removed reference to components of the study interventions being monoclonal antibodies | One injection for those assigned to AZD3152 will be placebo |
| 4.2.2 Rationale for Study Population | Changed references to AZD5156 to AZD3152 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 4.3.1 Justification for AZD5156 Dose | Noted that AZD5156 will be administered in the Sentinel Safety Cohort | Clarification |
| 4.3.4 Justification for Placebo | Added details of administration of placebo that will be included with AZD3152 to maintain the blind | One injection for those assigned to AZD3152 will be placebo |
| 4.4 End of Study Definition | Noted that results from some laboratory samples may not become available until after the study completion date | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | AZD3152 is now included | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.1 Randomization | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 6.3.2 Blinding | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.2 Blinding | Added AstraZeneca Bioanalytical monitor and unblinded Biometric teams to the list of those who will have access to the randomization list during the study | Clarification |
| 7.1 Discontinuation of Study Intervention | Section adjusted to mention AZD3152 instead of AZD5156 for the Main Cohort, also added clarification about process if participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Noted that AstraZeneca will make the final decision on a temporary hold after analysis of the safety data | Clarification |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | Clarified that study would be put on temporary hold if Grade 3 or higher AEs were reported for at least 2 participants (and not simply when 2 Grade 3 or higher AEs were reported) | Wording made consistent with previous AZD7442 studies |
| 8.2.2 Vital Signs | The timing of the vital signs assessments will specifically be 10 to 15 minutes after both injections (ie, the word 'approximately' has been removed) | Clarification regarding the time around vital signs collection |
| 8.2.4 Clinical Safety Laboratory Assessments | Removed reference to Laboratory Manual | Not applicable |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that glucose assessment is specifically glucose (random), and added pregnancy test and FSH to the table of variables | Clarification |
| 8.2.4 Clinical Safety Laboratory Assessments | Added clarifications around pregnancy testing. Furthermore, the FSH evaluation no longer applies only to those in the Sentinel Safety Cohort. | Clarification |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Reiterated that SAEs, MAAEs, and AESIs will be collected throughout the study | Clarification |
| 8.3.4 Adverse Events of Special Interest | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.3.9 Reporting of Serious Adverse Events | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.1 Pharmacokinetics | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.5.2.1 Anti-drug Antibody Assessments | Section adjusted to mention AZD3152 as well as AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 8.6.2 Other Study-Related Biomarker Research | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.1 General Considerations | Description of study updated to reflect change of strategy in terms of using AZD3152 alone | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.2 Efficacy | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.4.6 Pharmacokinetics | Order of paragraphs reversed, so that Sentinel Safety Cohort is discussed first, text regarding Main Cohort updated to reference AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |
| 9.5 Planned Analyses | Removed text regarding an emerging VOC significantly affecting the neutralization activity of AZD7442 | Updated information, as there is a possibility that the situation described in the deleted text may have already occurred |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.7 Data Safety Monitoring Board – Main Cohort | Section adjusted to mention AZD3152 instead of AZD5156 | AZD3152 will be developed as a standalone therapy, rather than as part of the AZD5156 combination therapy |

**CSP Version 4.0 [16 January 2023]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to add efficacy as a secondary endpoint to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the Main Cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy of AZD5156 compared with AZD7442. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

The protocol has also been amended to enhance the safety assessments of the Main Cohort, at the request of a Regulatory Authority.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1; noted that the test must return a negative result before dosing | To align with internal guidance for WOCBP |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total) |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Additional assessments of vital signs have been added on Days 8 and 189 of the Main Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Pregnancy test added at Visit 1, with the timing specified as prior to randomization | To align with internal guidance for WOCBP (pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization) |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Sample for serum chemistry, hematology, coagulation (local laboratory) will be collected on Days 1, 8, and 29; noted that this assessment is to be performed for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of troponin at screening for the Main Cohort | To increase cardiac safety monitoring |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Added the footnote clarifying that home or mobile visits by study staff may substitute for site visits to the Day 1 Illness Visit as well | To ensure sites can perform the Day 1 Illness Visit at home, if needed |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e-Diary and training has been added, along with Investigator site review of e-Diary entry completion | Clarification and for consistency |
| 3 Objectives and Endpoints | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP administration (was previously to Day 29) | For both cohorts, the collection period for AEs has been increased from 28 to 90 days after each dose of study intervention |
| 3 Objectives and Endpoints | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3 Objectives and Endpoints | References to dominant variants removed | To make the objectives/endpoints less specific |
| 3 Objectives and Endpoints | nAb responses to variant BA.2 will be evaluated | To include current and emerging variants of concern |
| 3 Objectives and Endpoints | Addition of secondary endpoint related to efficacy | Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case will be evaluated as a secondary endpoint |
| 3 Objectives and Endpoints | For the objective '*To characterize the cellular immune responses to SARS-CoV-2*' the following endpoint has been added: *Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing* | To further characterize the cellular immune response |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated.<br>This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total) |
| 4.1 Overall Design | The collection period for AEs has been increased from 28 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow up |
| 4.1 Overall Design | Noted that MAAEs will be collected throughout the study | Consistent with added safety endpoint |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #4 has been deleted | Duplication with the original inclusion #7 |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11 (original exclusion #10), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15 (original exclusion #14), hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #3 (original inclusion #4) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on negative rapid antigen test at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Inclusion #4 (original inclusion #5) will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 5.2.1 Inclusion Criteria (Main) | Text regarding participants with cancer in Inclusion #5 (original inclusion #6) has been updated to clarify that those with solid tumor cancer who are included in the study must be on active treatment, excluding the exceptions noted; hematologic malignancy has now been noted as a separate risk factor | This was a Regulatory Authority request |
| 5.2.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within at least 2 weeks prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12 (original exclusion #11), window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Subsection on stopping rules for Main Cohort removed | Replaced with new section on Study Suspension/Early Termination |
| 7.4 Study Suspension/Early Termination | New section | Added for consistency with wording used in AZD7442 studies |
| 8.2.3 Electrocardiograms | New section | Added to describe procedures for ECG |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted that serum chemistry, hematology, coagulation (local laboratory) assessments will be conducted for at least the first 600 participants in the Main Cohort; deleted text stating that clinical safety laboratory assessments will not routinely be performed for the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted (in Table 11) that troponin assessment will be performed in the Main Cohort at screening | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1.1 Determination of Drug Concentration | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.6.2.1 Assessment of Cell-mediated Immune Responses | New section | For consistency with endpoints section |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.7 Data Safety Monitoring Board – Main Cohort | Added MAAEs to the safety parameters that will be assessed as part of the DSMB review | Consistent with MAAEs having been added as a safety endpoint |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | Updated footnote to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 1.3 Schedule of Activities | Updated text describing the duration of treatment and follow-up periods from 12 months to 15 months | To reflect the change to the study design to increase the safety collection time |
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Moved the footnote marker for vital signs assessments from dosing days to the overall row header as abnormal vital signs must be repeated at all scheduled vital signs assessments, and not only on dosing days, after the participant has been at rest for at least 5 minutes | Correction for consistency with vital signs assessments for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The numbers of confirmed cases and deaths due to COVID-19 have been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'currently circulating Omicron variants' has been replaced with 'past Omicron variants' | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term 'ADE disease' has been replaced with 'ADE of infection' | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Specified that cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies | Clarification that these events will be monitored in other AZD5156 studies in addition to the present study |
| 2.3.2 Benefit Assessment | Noted that similarity of AZD5156 to AZD7442 is in terms of structure and mechanism of action | Clarification |
| 2.3.2 Benefit Assessment | Noted that AZD7442 and AZD5156 may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus | Clarification |
| 3 Objectives and Endpoints | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative RT-PCR at baseline to positive at any time up to 6 and 12 months | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 3 Objectives and Endpoints | Minor change to endpoint describing how exploratory samples may be used to align with change in Section 8.5.2.3 | Clarification |
| 4.1 Overall Design | Added that the safety and neutralizing activity of AZD5156 will be compared with AZD7442 for pre-exposure prophylaxis of | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | COVID-19 and that the study will be conducted globally | |
| 4.1 Overall Design | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.1 Overall Design | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1 Overall Design | Added that immediate AEs will be collected for a 1-hour observation period after study intervention administration | Clarification |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Updated text to provide further information on ESDRs | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.2 Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| 4.2 Scientific Rationale for Study Design | Noted that a dose exploration study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.1 Rationale for Administration Site | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions | To further clarify rationale for the administration site |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the threshold (was $IC_{90}$ now $IC_{80}$) | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.1 Inclusion Criteria (Sentinel) | For inclusion #6, clarified that participant must understand and comply with all study requirements/procedures | Clarification |
| 5.2.1 Inclusion Criteria (Main) | For inclusion #7, clarified that participant must understand and comply with all study requirements/procedures (including those at Illness Visits) | Clarification |
| 5.4 Screen Failures | Criteria for rescreening have been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated in the text and in a footnote to Table 8 | Updated to reflect current information |
| 6.1 Study Intervention(s) Administered | Noted in the text and in a footnote to Table 8 that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive the first component of their assigned intervention will all receive the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Added specific details for placebo | Clarification |
| 6.1 Study Intervention(s) Administered | Noted in Table 8 that L-histidine hydrochloride is monohydrate | Clarification |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage and administration of IMP | Wording added to provide more comprehensive details of IMP storage and administration |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.1 Randomization | Added text that participants will receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention, and those having access to the randomization list during the study | Clarification |
| 6.3.2 Blinding | Removed text about Investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.5 Concomitant Therapy | Minor update to wording regarding the Concomitant Medication eCRF | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the 'Restricted' section in Table 9 | To ensure the correct patient population is enrolled |
| 8 Study Assessments and Procedures | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 8.1.2 Participant-reported COVID-19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | Extra information added regarding e-Diaries and documentation in the eCRF | Updated for clarity |
| 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments | Added text stating that genotypic sequencing analysis and phenotypic characterization would be of SARS-CoV-2 Spike protein mutations rather than of the virus | Clarification |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment, and noted that any observations will | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | be documented in the participant's medical records | |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.4 Clinical Safety Laboratory Assessments | Clarified that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 8.2.4 Clinical Safety Laboratory Assessments | Included the option for urea results to be reported as blood urea nitrogen, and for prothrombin time results to be reported as international normalized ratio | Clarification |
| 8.2.5.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.5.2 Injection Site Reactions | Noted that diameters of any redness/swelling may be recorded at site visits | Clarification |
| 8.2.5.2 Injection Site Reactions | Removed references to specific time points for the Sentinel Safety Cohort | Those specific details were not needed because reference is made to the SoAs |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | Noted that AESIs will be programmatically identified through AE information that is collected in the eCRF | Clarification |
| 8.3.4 Adverse Events of Special Interest | Minor edits made throughout the section | Updated for clarity |
| 8.3.9 Reporting of Serious Adverse Events | Minor change to wording of statement about reporting of SAEs | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.3.11.1 Timelines | Updated wording for SAEs associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.2.3 Additional Serum Immunogenicity | Minor change to statement regarding how exploratory serum samples may be used | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.3 Populations for Analyses | Updated the definition of the SARS-CoV-2 neutralizing antibody analysis set to remove the text 'with quantifiable SARS-CoV-2 serum titers' | This was a Regulatory Authority request related to the inclusion of participants without quantifiable serum titers but who received investigational product |
| 9.3 Populations for Analyses | Updated the definition of the anti-drug antibody analysis set | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.1 General Considerations | Noted that details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses | Clarification |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.4.2 Efficacy | Deleted reference to 'incidence of post treatment COVID-19' as 'incidence of post treatment symptomatic COVID-19' is already specified | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses | Clarification that nAb responses against additional Omicron variants such as BA.2 will be evaluated | To include current and emerging variants of concern |
| 9.4.4 Anti-drug Antibody Variables | Text regarding anti-drug antibody variables edited, with a reference added to the SAP | To simplify the text to keep the necessary information and refer to the SAP for further details |
| 9.5 Planned Analyses | Added details of analyses for Sentinel Safety Cohort | Clarification |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | team will remain blinded during primary analysis | |
| 9.5 Planned Analyses | Noted that an evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID 19 be observed prior to the final analysis | Clarification |
| 9.7 Data Safety Monitoring Board – Main Cohort | Updated text to clarify that Day 15 safety data review in adult Main Cohort participants will be in at least 40 participants, and not approximately 40 participants, who have received AZD5156 | Clarification |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore, have not been summarized |

**CSP Version 3.0 [09 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort, at the request of a Regulatory Authority.

**Summary of Change**s:

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory | This has been added to assist with making a decision regarding whether a female participant is |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | assessments at screening for the Sentinel Safety Cohort | postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination, vital signs, and injection site reaction monitoring (local reactogenicity) have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Sample for clinical safety laboratory assessments added at Day 1 (predose) for the Sentinel Safety Cohort | To obtain baseline values |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For the vital signs assessment on Day 1 of the Sentinel Safety Cohort, the indicator '(predose)' has been deleted | This has been deleted for reasons of clarity, because Day 1 vital signs are not only assessed predose, and the existing footnote (a) provides specific details of the timings |

**CSP Version 2.0 [02 December 2022]**

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

**Overall Rationale for the Modification:**

The protocol has been amended primarily to enhance the safety assessments of the study at the request of a Regulatory Authority, who acknowledged the similarities between EVUSHELD and AZD5156, but noted that this was the first-in-human study for the AZD3152 component of AZD5156.

Note: due to a typing error, the word 'imitating' appears several times instead of 'initiating' in this historical Summary of Changes, and reference is made to the fact that '*no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed*'; this should have read 80 adult Main Cohort participants.

**Summary of Changes:**

**List of Substantial Modifications**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | A screening period has been added for the Main Cohort. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram has been added as a screening assessment for the Sentinel Safety Cohort | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be collected at the Day 15 visit for the Sentinel Cohort | To facilitate the ESDR of the Day 15 data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 40 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1.1 Part A Sentinel Safety Cohort | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A Main Cohort and Part B | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.3.2 Exclusion Criteria (Part B) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort | An additional stopping criteria has been added: two or more Grade 3 adverse drug reactions, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca. | This was a Regulatory Authority request |
| 7.2.2 Stopping Rules for Part A Main Cohort and Part B | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.6 Safety Review Committee | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Footnote (c) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Part A: Main Cohort and Part B Participants | Footnote (f) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (e) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the present study | Clarification |
| 4.1.1 Part A Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.3 Clinical Safety Laboratory Assessments | The timing of the pregnancy tests for the Main Cohort have been adjusted | The Main Cohort now has a screening visit |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | AZD5156 |
| Study Code | D7000C00001 |
| Version | 1.0 (Local CSP 1 United States) |
| Date | 30Nov2022 |

# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version: 1.0 (Local CSP 1 United States)

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator; and placebo (0.9% sodium chloride for injection)

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Short Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 1.0 / Local CSP 1 United States | 30-Nov-2022 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 1.0 / Local CSP 1 United States [30 November 2022]

This modification is considered to be substantial due to the number of substantial changes introduced, as detailed below.

### Overall Rationale for the Modification:

The addition of efficacy as a secondary endpoint to provide clinical efficacy to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the main cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram added at screening | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Added assessment of troponin | To increase cardiac safety monitoring |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1 | To align with internal guidance for WOCBP |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Laboratory safety testing added at Visit 1 | To obtain baseline values |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | An additional assessment of injection site reactions has been added at Day 8 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total). |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 1.3.3 Treatment and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e Diary and training has been added | Clarification |
| 3 OBJECTIVES AND ENDPOINTS | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP administration (was previously to Day 29) | For both cohorts, the collection period for AEs has been increased from 29 to 90 days after each dose of study intervention |
| 3 OBJECTIVES AND ENDPOINTS | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |
| 3 OBJECTIVES AND ENDPOINTS | Additional details added to the secondary endpoint related to efficacy | With the increased sample size the secondary endpoint, symptomatic COVID-19, is expected to be appropriately powered to test efficacy and support the use of AZD5156 in the pre-exposure prophylaxis setting |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated, and all references to a specific Part B of the study have been deleted.<br>This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total). |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | The number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |
| 4.1 Overall Design | Noted that dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 4.1 Overall Design | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.1 Sentinel Safety Cohort | The ratio of participants receiving AZD5156 or placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.3 Safety Review | Section updated | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #3 has been deleted | Duplication with the original inclusion #6 |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within 3 months prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11, window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15, hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within 3 months prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12, window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 or placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 or placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.5 Concomitant Medication | Noted that, for the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy. | Clarification |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | An additional stopping criteria has been added: two or more severe adverse drug reactions, regardless of type. | This was a Regulatory Authority request |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2.2 Stopping Rules for Main Cohort | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 8.2.3 Clinical Safety Laboratory Assessments | Added assessment of troponin at screening only | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1 Pharmacokinetics | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | The number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.6 Safety Review Committee - Sentinel Safety Cohort | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board – Main Cohort | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Footnote (d) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Treatment and Follow-up Activities –Main Cohort Participants | The timing of the Visit 1 assessment has been changed from predose to prior to randomization | Pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization. |
| 1.3.3 Treatment and Follow-up Activities – Main Cohort Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Treatment and Follow-up Activities – Main Cohort Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Treatment and Follow-up Activities – Main Cohort Participants | Footnote (e) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (d) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The number of confirmed cases of COVID-19 has been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term ‘currently circulating Omicron variants’ has been replaced with ‘past dominant variants’ | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term ‘ADE disease’ has been replaced with ‘ADE of infection’ | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term ‘ADE disease’ has been replaced with ‘ADE of infection’ | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the AZD5156 studies | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.2 Scientific Rationale for Study Design | Noted that a dose ranging study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.4 Screen Failures | Criteria for rescreening has been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive then first component of their assigned intervention will all received the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated | Updated to reflect current information |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage of IMP | Wording added to provide more comprehensive details of IMP storage |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.2 Blinding | Removed text about investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention | Clarification |
| 6.5 Concomitant Therapy | Added that intravenous immunoglobulin infusion for participants with common variable immunodeficiency is a permitted concomitant medication | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the restricted section of the table | To ensure the correct patient population is enrolled |
| 7.2.2 Stopping Rules for Main Cohort | Replaced some of the existing text with text about the DSMB | Updated to reflect the addition of a DSMB for the Main Cohort |
| 8 STUDY ASSESSMENTS AND PROCEDURES | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.2 Participant reported COVID--19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment | Clarification |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.3 Clinical Safety Laboratory Assessments | Details of timing of pregnancy tests updates | The Sentinel Safety Cohort now has a test at Visit 1 |
| 8.2.4.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should occur in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.4.2 Injection Site Reactions | Noted that diameters of any redness/swelling will be recorded | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.3.11.1 Timelines | Updated wording for SAE associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study team will remain blinded during primary analysis | Clarifications |
| 9.6 Safety Review Committee - Sentinel Safety Cohort | Clarified that this will now only apply to the Sentinel Safety Cohort | Required due to removal of the concept of study having Parts A and B |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| BSSR | Blinded sample size re-estimation |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| GCP | Good Clinical Practice |

| Abbreviation or special term | Explanation |
|---|---|
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{XX}$ | Concentration required for XX% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoA | Schedule of activities |

| Abbreviation or special term | Explanation |
|---|---|
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha, and the demonstration of efficacy of AZD5156 compared to EVUSHELD.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the efficacy of AZD5156 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other noninvestigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD5156 vs AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD5156 compared with AZD7442 for pre-exposure prophylaxis of COVID-19.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort.

The Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded to study intervention). Participants from the Main Cohort will receive a second dose of their assigned study intervention, approximately 6 months after their first dose.

**Number of Participants:**

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: single dose of AZD5156 600 mg IM or AZD7442 600 mg IM.

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Sentinel Safety Cohort after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b) of the Sentinel Safety Cohort, and subsequently prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded

manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. This review will be based on preliminary data that will have not been subject to validation and DBL.

**Statistical Methods**

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants' data will be presented by the dosing regimen received.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

No interim analyses are planned. The primary analyses will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end-of-study visit.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will be evaluated.

Efficacy Endpoints

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazard model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD5156 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented.

Other COVID-19 efficacy endpoints are derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

Characterization of PK

Following initial dosing with AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

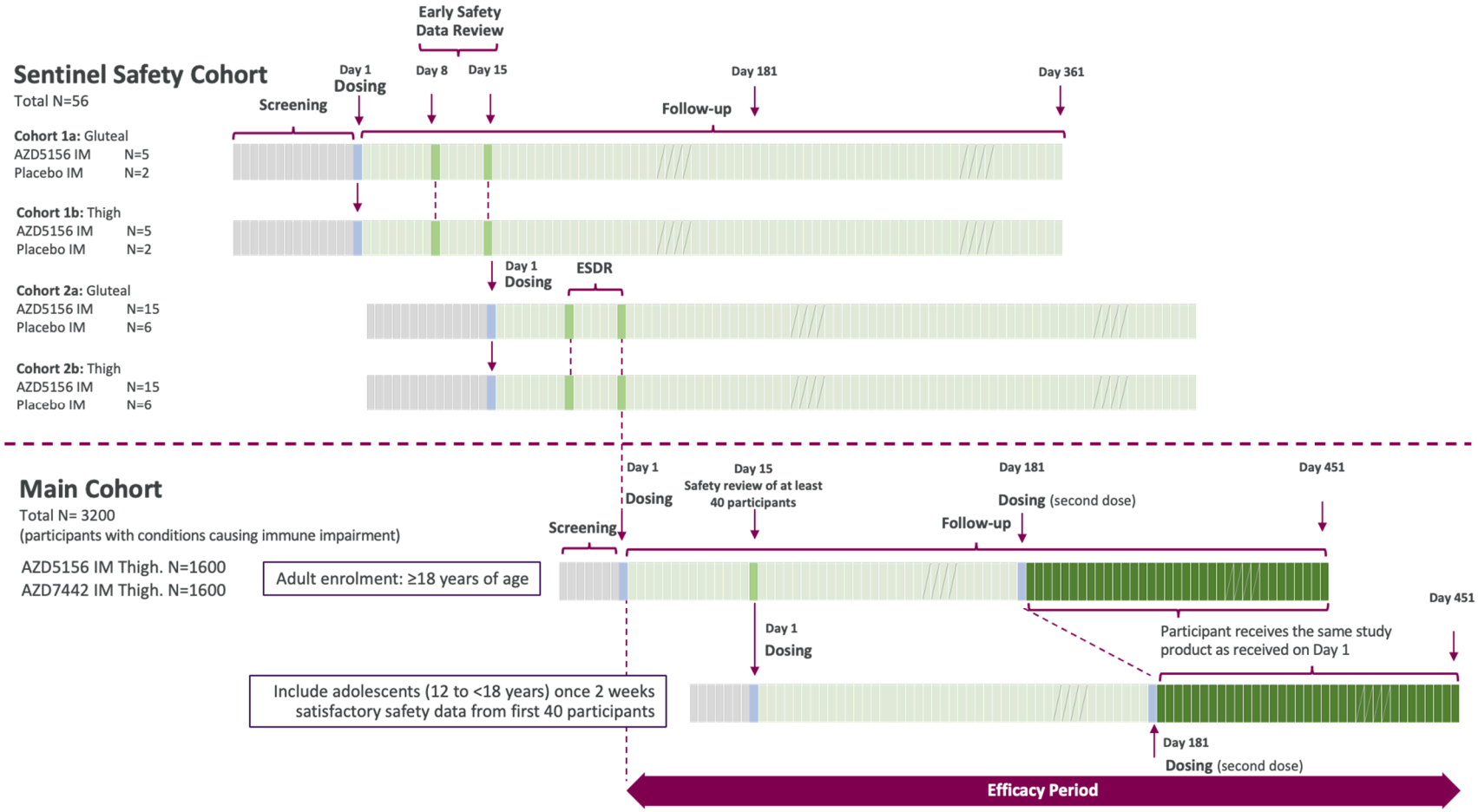
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 7 days (Day -7 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| Electrocardiogram (single) | X |
| Serum chemistry, hematology, coagulation (local laboratory), troponin T/I | X |
| Urine pregnancy test [a] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Pregnancy test must be negative at screening
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | | | | | | | | | | | |
| Vital signs [a] | X | | | | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory)[d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) [f] | X | | | X | | | | | | | | |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10[b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | | | | | | | X |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [c] | X | X | | | | | X | | | | | | |
| Electrocardiogram (single) | X | | | | | | | | | | | | |
| Urine pregnancy test (WOCBP only, local laboratory) [d] | X | X (prior to randomization) | | | | | X (predose) | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [e] | | X (predose) | | | | | X (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [f] (predose) | | | | | X [f] | | | | | | |

## Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10[b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [g] | | X ← → | | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |
| PK serum sample [h] | | X (predose) | | | X | X | X (predose) | X | X | X | X | | X |
| PK nasal lining fluid sample [i] | | X (predose) | | | X | X | | | | | | | |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [j] | X | | | | X [j] | X | | | | | |
| Immediate AEs [k] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[d] Sample urine test must return a negative result before dosing.
[e] Sites will be provided with rapid antigen tests.
[f] To be collected at baseline. The results are not needed prior to dosing.
[g] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[h] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[i] The nasal lining fluid sample will be collected only for the first 1200 participants (approximately) in the Main Cohort.
[j] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[k] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that it is appropriate to do so.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE =medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Assessment of AEs, SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Set up of e-Diary and training | X | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Saliva sample for viral shedding | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [d] | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results will not be reported to sites.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.
AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE =medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD5156 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles, nAb titer responses to SARS-CoV-2 Alpha, and the demonstration of efficacy of AZD5156 compared to EVUSHELD.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 17 November 2022, has caused over 630 million confirmed cases of COVID-19, including more than 6.5 million deaths, reported to the WHO (WHO 2022). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the past dominant Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in

AZD5156 has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2 spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, and BF.7 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is

provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. The disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry, is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## Table 5 Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the efficacy of AZD5156 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other noninvestigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD5156 vs AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit. |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD5156 compared with AZD7442 for pre-exposure prophylaxis of COVID-19. The study will be conducted globally.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort.

The Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh. Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so (for more details on the safety review, see Sections 4.1.1 and 4.1.3). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be

administered as 2 sequential IM injections, one injection for each mAb component. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first 56 participants in the study will comprise the Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants

The ESDR for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- An initial ESDR will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1 and 1b (a total of 14 participants) of the Sentinel Safety Cohort. During the initial ESDR, enrollment of participants will be paused. If the ESDR concludes that it is appropriate, then enrollment will be permitted to continue and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- A further ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile.

The safety data collected will be entered into eCRFs and reviewed. This review is based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDR:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

For more details on the ESDR, see Section 4.1.3.

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a

(Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156).

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (1600) | AZD7442 600 mg (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Sections 4.1.1and 9.6.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

A dose ranging study will be conducted separately to the present study.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers

compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Main Cohort participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase 3 studies. Given the expected safety and PK profile of AZD5156, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD5156 clinical development plan. The adolescent population was approved for EVUSHELD based on the PK extrapolation.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442

serum concentrations exceed the modeled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

### 4.3.3 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals at low risk of development of severe COVID-19 in order to maintain the double-blind in the Sentinel Safety Cohort and also better objectively assess the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the AZD7442 Phase I study (D8850C00001).

## 4.4 End-of-Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
   – Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

– Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

– The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

– All female participants of childbearing potential must have a negative urine pregnancy test result at screening.

– Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral within 3 months prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test at Visit 1.

4 Weight ≥ 40 kg at Visit 1.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have cancer (eg, active solid tumors and hematologic malignancies) except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

6 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation,

symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral within 3 months prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure, unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitute the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive only cell pools material. In the Main Cohort, participants may receive either cell pools material or clonal cell material.

The AZD1061 component of AZD5156 for the Sentinel Safety Cohort will initially be supplied from the AZD7442 clonal cell material. A more concentrated formulation of the clonal cell material for AZD1061 will be administered to participants in the Main Cohort. In the Main Cohort, participants may receive either the initially supplied AZD7442 material or the more concentrated material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort and the Main Cohort utilizing AZD3152 cell pool material and initially supplied AZD1061 material, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD5156 in the Main Cohort utilizing AZD3152 clonal cell material and the more concentrated AZD1061 formulation, label-claim volume per vial is 2 mL for each component. For AZD7442 in the Main Cohort, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 IM injections, one injection for each component mAb. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895. This will ensure that all participants who only receive the first component of their assigned intervention will all received the same component (AZD1061).

**Table 8 Investigational Medicinal Products**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort and Main Cohort[a]** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort[b]** | **AZD7442 (AZD1061 + AZD8895) for Main Cohort** | **Placebo for Sentinel Safety Cohort** |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain either 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain either 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration** | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections (thigh) of 2 mL each | 2 IM injections (thigh) of 3 mL each | 2 IM injections (gluteal or thigh): 3 mL and 2 mL |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] In the Main Cohort, for the AZD3152 component, participants may receive cell pools material and for the AZD1061 component, participants may receive the initially supplied AZD7442 formulation (as shown in the column).

[b] In the Main Cohort, for the AZD3152 component, participants may receive clonal cell material and for the AZD1061 component, participants may receive the more concentrated formulation (as shown in the column).

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature-monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156 and AZD7442 for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (that is, the individual storage time limits are not additive). AZD5156 and AZD7442 do not contain

preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system
- The AstraZeneca supply chain department

- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Intravenous immunoglobulin infusion for participants with common variable immunodeficiency | |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals should not be given within 3 months prior to Visit 1. COVID-19 antivirals should also not be given during the study until after the Day 29 assessments. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to Visit 1. |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD5156 or AZD7442), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose. For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 or Section 7.2.2 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.

- Any two Grade 3 or higher AEs, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Main Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the Main Cohort) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including

those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, the Omicron variant BA.4/5, and the emerging dominant variant circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week. For participants in the Main Cohort, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must be advised to contact the study site as soon as possible.

For participants in the Sentinel Cohort, if SARS-CoV-2 symptoms are reported, an Illness Visit is not required. The participant should be instructed to seek care via their usual healthcare provider.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Main Cohort will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the participant will be instructed to stop all Illness Visit assessments and home laboratory kits and

will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in an Illness e-Diary. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.3).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of virus identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.

- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort only (see Section 1.3.1 and Section 1.3.2). Clinical safety laboratory assessments will not routinely be performed for the Main Cohort.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T/I (Sentinel Cohort screening only) |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts), Visit 1 (both cohorts), and Visit 5 (Main Cohort only). The test must be negative before dosing.

## 8.2.4 Other Safety Assessments

### 8.2.4.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in

accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.4.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling will be recorded.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following administration of study intervention. Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer

'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156 and AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Medically Attended Adverse Events

MAAEs will be collected according to the time points specified in the SoAs (Section 1.3).

MAAEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2

infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs.

Where AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.10.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital

anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, nasal lining fluid samples will be collected only for the first 1200 participants (approximately). Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs –Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory

operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants' data will be presented by the dosing regimen received.

## 9.1 Statistical Hypotheses

The primary objectives are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442.

A BSSR may be conducted prior to the primary analysis. The overall symptomatic COVID-19 event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed. Full details will be in a BSSR plan.

The sample size in the Main Cohort is driven by the total number of events required to demonstrate the efficacy of AZD5156 versus AZD7442 in the prevention of symptomatic COVID-19. A minimum of 40 events will provide at least 90% to detect HR of 0.3, or a 70% reduction in hazard. Under the assumption that the event rate will be approximately 3.2% AAR in the AZD7442 arm, HR of 0.30 (70% efficacy), significance level of $\alpha$=0.05, and 10% attrition. A target sample of approximately 3200 participants has been selected to reach the required number of events assuming participants were observed for 8 months or more. Assumptions are based on data from prior studies with AZD7442 and reported estimates of the AAR among those with immunocompromising conditions (Kelly et al 2022).

A sample size of approximately 1200 participants in the Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

The main cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD5156 compared with 1600 participants receiving a US EUA granted and EU MAA approved active comparator, AZD7442.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Anti-drug antibody analysis set | All participants in the FAS with baseline and postdose anti-drug antibody results. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |
| Immunobridging analysis set | Participants in the FAS who have a baseline and post intervention Day 29 antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

This study is designed to evaluate the immunobridging, efficacy, and safety of AZD5156 compared with AZD7442. The primary endpoint is a noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received. Methods for controlling multiplicity across endpoints will be presented separately in the SAP for the immunobridging and efficacy analyses.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses.

### 9.4.2 Efficacy

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops symptomatic COVID-19 at any time up to Visit 9 (12 months). Positive cases require a central RT-PCR test and meet the qualifying symptoms satisfying the modified WHO definition of symptomatic COVID-19 (see Section 8.1.2).

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazard model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD5156 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Participants who become unblinded to treatment assignment and/or take other noninvestigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding or receipt of the first dose of COVID-19 preventive product. Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and will be included in the analysis. Participants that withdraw early from the study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

Other efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

- Incidence of post-treatment COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will also be evaluated. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Anti-drug Antibody Variables

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total number of participants with negative ADA assay response at all times
- Total number of participants with positive ADA assay response at any time
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response

at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels

- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay
- Titer values
- Titer category

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following initial dosing with AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

## 9.5 Planned Analyses

No interim analyses are planned. The primary analyses will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end-of-study visit. An evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID-19 be

observed prior to the final analysis. The study will maintain a double-blind period until the primary analysis. To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan; the study team will remain blinded. Participant-level unblinding information will be kept strictly confidential, and the rationale for any unblinding will be documented. The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee - Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Sentinel Safety Cohort, as discussed in Section 4.1.3.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. This review will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of the first 80 adult participants (approximately 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrolment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person

- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

## C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

(a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

(b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 13, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

| | | |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

| | | |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care

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# SIGNATURE PAGE

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# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Version: 1.0 (Local CSP 2 United States)

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator; and placebo (0.9% sodium chloride for injection)

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym and Short Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 1.0 / Local CSP 2 United States | 20-Dec-2022 |
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## CSP Version 1.0 / Local CSP 2 United States [20 December 2022]

This modification is considered to be substantial due to the introduction of additional safety assessments, as detailed below.

## Overall Rationale for the Modification:

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort and the Main Cohort, at the request of a Regulatory Authority.

## Summary of Changes:

## List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Removed troponin assessment at screening for the Sentinel Safety Cohort | Based on the decision that troponin assessments at screening were not needed in the healthy, adult participants enrolled in the Sentinel Safety Cohort |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Additional assessments of targeted physical examination and vital signs have been added on Days 3, 5, and 8 of the Sentinel Safety Cohort; injection site reaction monitoring (local reactogenicity) has been added on Days 3 and 5 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | A sample for serum chemistry, hematology, coagulation (local laboratory) will now also be | To facilitate the ESDR of the Day 15 data |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | collected at the Day 15 visit for the Sentinel Cohort | |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Additional assessments of vital signs have been added on Days 8 and 189 of the Main Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Sample for serum chemistry, hematology, coagulation (local laboratory) will be collected on Days 1, 8, and 29; noted that this assessment is to be performed for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants | Added assessment of troponin at screening for the Main Cohort | To increase cardiac safety monitoring |
| 5.2.1 Inclusion Criteria | The inclusion criterion of weight ≥ 40 kg will now also be assessed at Visit 5 in addition to Visit 1 | To verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that serum chemistry, hematology, coagulation (local laboratory) assessments will be conducted for at least the first 600 participants in the Main Cohort | This was a Regulatory Authority request to perform clinical safety laboratory assessments for at least the first 600 participants in the Main Cohort |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted (in Table 11) that troponin assessment at screening will be performed in the Main Cohort | To increase cardiac safety monitoring |
| 8.2.3 Clinical Safety Laboratory Assessments | Removed (from Table 11) troponin assessment at screening for the Sentinel Safety Cohort | Based on the decision that troponin assessments at screening were not needed in the healthy, adult participants enrolled in the Sentinel Safety Cohort |
| 8.2.3 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening for the Sentinel Safety Cohort | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |
| 8.2.4.2 Injection Site Reactions | Noted that assessments will now be performed on Days 3, 5, and 8 of the Sentinel Safety Cohort | This was a Regulatory Authority request to increase the frequency of some safety assessments |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3 Objectives and Endpoints | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative RT-PCR at baseline to positive at any time up to 6 and 12 months | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |
| 4.1 Overall Design | Noted that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.2.1 Rationale for Administration Site | Noted that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce risk of local site reactions | To further clarify rationale for the administration site |
| 6.1 Study Intervention(s) Administered | Noted in the text and in a footnote to Table 8 that the second injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 6.5 Concomitant Therapy | Noted (in Table 9) that COVID-19 antivirals could be administered as standard of care treatment for participants in the Main Cohort who developed COVID-19 | This was a Regulatory Authority request for consistency within Section 6.5 as COVID-19 antivirals would be considered standard of care treatment for any participants in the Main Cohort |
| 8.2.3 Clinical Safety Laboratory Assessments | To clarify that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 9.3 Populations for Analyses | Updated the definition of the SARS-CoV-2 neutralizing antibody analysis set to remove the text ‘with quantifiable SARS-CoV-2 serum titers’ | This was a Regulatory Authority request related to the inclusion of participants without quantifiable serum titers but who received investigational product |
| 9.4.2 Efficacy | Updated references to incidence of COVID-19 to incidence of symptomatic COVID-19 for participants with negative | This was a Regulatory Authority request for clarification as COVID-19 refers to SARS-CoV-2 infection with symptoms |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | RT-PCR at baseline to positive at any time up to 6 and 12 months | |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore, have not been summarized |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AAR | Annualized attack rate |
| ADA | Anti-drug antibody |
| ADE | Antibody dependent enhancement |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| BSSR | Blinded sample size re-estimation |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |

| Abbreviation or special term | Explanation |
|---|---|
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| HR | Hazard ratio |
| $IC_{XX}$ | Concentration required for XX% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limit |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |

| Abbreviation or special term | Explanation |
|---|---|
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha, and the demonstration of efficacy of AZD5156 compared to EVUSHELD.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the efficacy of AZD5156 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other noninvestigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD5156 vs AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD5156 compared with AZD7442 for pre-exposure prophylaxis of COVID-19.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort.

The Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For

AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety, immunogenicity, and efficacy study, comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded to study intervention). Participants from the Main Cohort will receive a second dose of their assigned study intervention, approximately 6 months after their first dose.

**Number of Participants:**

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442.

**Intervention Groups and Duration:**

Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Main Cohort: single dose of AZD5156 600 mg IM or AZD7442 600 mg IM.

The duration of each participant's involvement in the study will be approximately 12 months (Sentinel Safety Cohort) or 15 months (Main Cohort) from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Sentinel Safety Cohort after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b) of the Sentinel Safety Cohort, and subsequently prior to enrollment of the Main Cohort.

**Data Safety Monitoring Board:**

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. This review will be based on preliminary data that will have not been subject to validation and DBL.

**Statistical Methods**

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants' data will be presented by the dosing regimen received.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

No interim analyses are planned. The primary analyses will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end-of-study visit.

*Primary Objectives*

The primary objectives are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments,

vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

SARS-CoV-2 nAb Response

The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will be evaluated.

Efficacy Endpoints

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazard model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD5156 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented.

Other COVID-19 efficacy endpoints are derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

Characterization of PK

Following initial dosing with AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

Evaluation of ADA

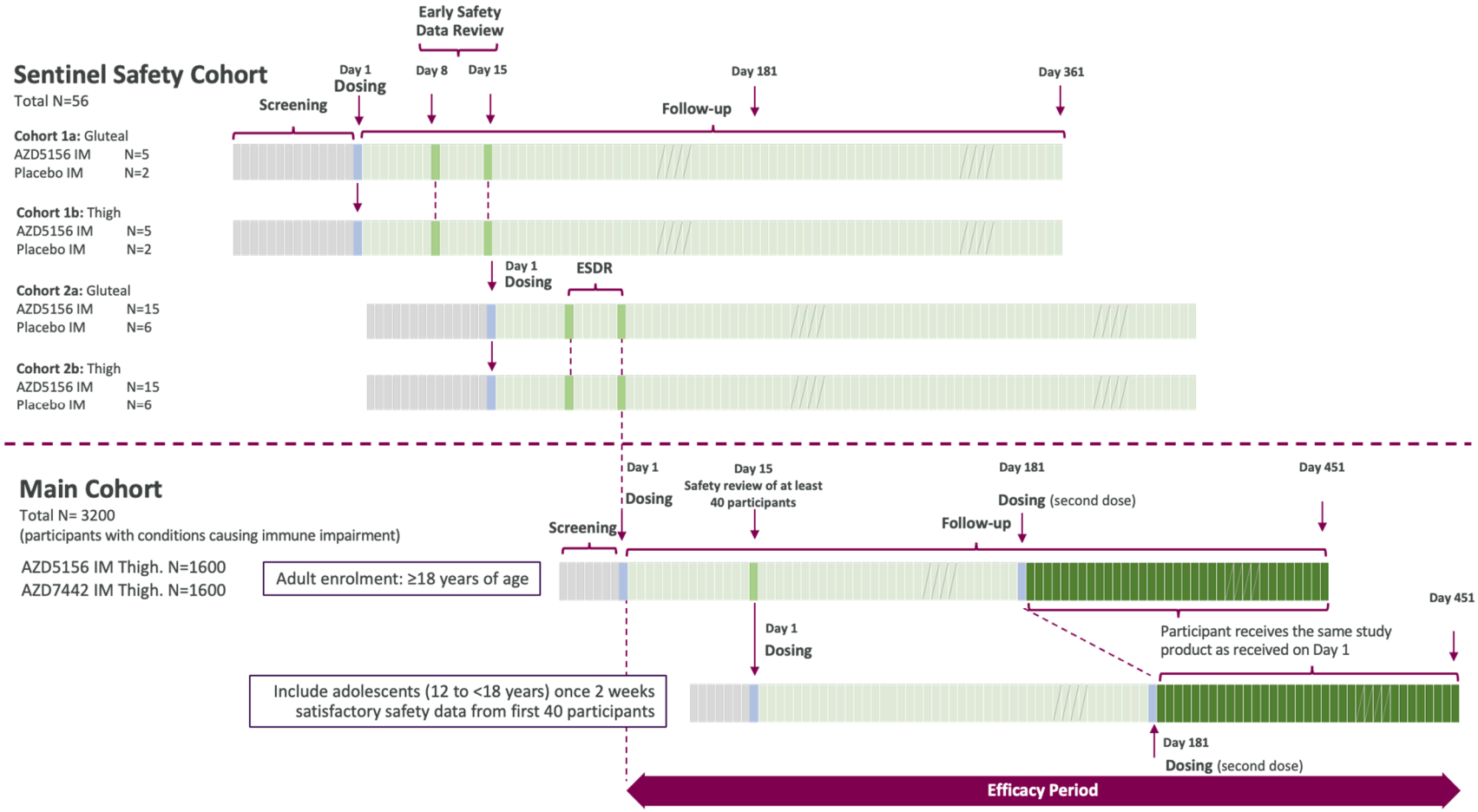
The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time

points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.

## 1.3 Schedule of Activities

For Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Main Cohort participants, there will be a screening period of up to 7 days (Day -7 through Day 1) and a treatment and follow-up period lasting 15 months after administration of study intervention at Visit 1 (Table 3).

For Main Cohort participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| Electrocardiogram (single) | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | X | X | X | | | | | | | | |
| Vital signs [a] | X | X | X | X | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory)[d] | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |
| Assessment of AEs | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Month** | **1** | **1** | **1** | **1** | **1** | **1** | **2** | **3** | **6** | **9** | **12** | |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Assessment of SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |
| Injection site reaction monitoring (local reactogenicity) | X [f] | X | X | X | | | | | | | | |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] Sample urine test must return a negative result before dosing.
[c] Sites will be provided with rapid antigen tests.
[d] To be collected at baseline; the results are not needed prior to dosing.
[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.3 Screening, Treatment, and Follow-up Activities – Main Cohort Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10[b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X (predose) | | | | | | |
| Randomization | | X (predose) | | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | | | | | | | X |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | | | | |
| Vital signs [c] | X | X | X | | | | X | X | | | | | |
| Electrocardiogram (single) | X | | | | | | | | | | | | |
| Urine pregnancy test (WOCBP only, local laboratory) [d] | X | X (prior to randomization) | | | | | X (predose) | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [e] | | X (predose) | | | | | X (predose) | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [f] (predose) | | | | | X [f] | | | | | | |

## Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10[b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| Serum chemistry, hematology, coagulation (local laboratory) [g] | | X | X | | X | | | | | | | | |
| Troponin T/I | X | | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [h] | | X ← → | | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X (predose) | | | | X | | X |
| PK serum sample [i] | | X (predose) | | | X | X | X (predose) | X | X | X | X | | X |
| PK nasal lining fluid sample [j] | | X (predose) | | | X | X | | | | | | | |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | | X |

## Table 3 Schedule of Activities (Treatment and Follow-up Period) – Main Cohort

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b[a]** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10[b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **1** | **3** | **6** | **6** | **7** | **9** | **12** | **15** | |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **± 15** | **NA** |
| **Study intervention administration** | | X | | | | | X | | | | | | |
| Injection site reaction monitoring | | X [k] | X | | | | X [k] | X | | | | | |
| Immediate AEs [l] | | X | | | | | X | | | | | | |

[a] This visit will only be required for the first 80 adult Main Cohort participants.
[b] Visit 10 will be completed by telephone.
[c] On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[d] Sample urine test must return a negative result before dosing.
[e] Sites will be provided with rapid antigen tests.
[f] To be collected at baseline. The results are not needed prior to dosing.
[g] To be performed for at least the first 600 participants in the Main Cohort.
[h] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[i] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[j] The nasal lining fluid sample will be collected only for the first 1200 participants (approximately) in the Main Cohort.
[k] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[l] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review at Day 15 concludes that it is appropriate to do so.

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE =medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Assessment of AEs, SAEs, MAAEs, and AESIs | X (ongoing observation and questioning) | | | | | |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Set up of e-Diary and training | X | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Saliva sample for viral shedding | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [d] | X | | | | | |
| NP swabs SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |

**Table 4 Schedule of Activities for Illness Visits (Main Cohort Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.

[d] A local and central RT-PCR test is required to be performed. The participant should continue with the Illness Visit schedule until the local RT-PCR test result confirms the participant is negative for SARS-CoV-2. If the local RT-PCR test cannot be performed for any reason, a rapid antigen test may be performed locally. Central RT-PCR laboratory test results will not be reported to sites.

Note: The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.
AE = adverse event; AESI = adverse event of special interest; IL-D = illness day; MAAE =medically attended adverse event; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD5156 to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles, nAb titer responses to SARS-CoV-2 Alpha, and the demonstration of efficacy of AZD5156 compared to EVUSHELD.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 17 November 2022, has caused over 630 million confirmed cases of COVID-19, including more than 6.5 million deaths, reported to the WHO (WHO 2022). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the past dominant Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in

AZD5156 has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2 spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE of infection. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, and BF.7 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is

provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known endogenous human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which constitutes half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. The disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry, is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE of infection occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established. Cardiovascular and thromboembolic events will continue to be routinely monitored in the AZD5156 studies.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar (structurally and in terms of mechanism of action) to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, and may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## Table 5 Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through 90 days after IMP administration<br>SAEs, MAAEs, and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the efficacy of AZD5156 to AZD7442 in the prevention of symptomatic COVID-19 | **Population**: Full Analysis Set<br>**Endpoint**: Time from the first dose of IMP to the first occurrence of a symptomatic COVID-19 case which is defined as:<br>• Negative RT-PCR at baseline to positive at any time up to Visit 9 (12 months) AND<br>• Satisfying modified WHO definition of symptomatic COVID-19<br>**Intercurrent events**: Participants who become unblinded to study intervention assignment and/or take other noninvestigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding/receipt of the first dose of COVID-19 preventive product, whichever is earlier, for the primary analysis.<br>**Summary measure**: Prophylactic efficacy, calculated as 1-HR (AZD5156 vs AZD7442) using a hazard regression model. |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit. |
| To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score ≥ 4)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; HR = hazard ratio; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 3256 participants to evaluate the safety and neutralizing activity of AZD5156 compared with AZD7442 for pre-exposure prophylaxis of COVID-19. The study will be conducted globally.

The study will consist of 2 cohorts: a Sentinel Safety Cohort and a Main Cohort.

The Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b) (Figure 1). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (up to Day 15) concludes that it is appropriate to do so (for more details on the safety review, see Sections 4.1.1 and 4.1.3). Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

The Main Cohort will enroll approximately 3200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of study intervention is administered.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections, one injection for each mAb component, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 150 sites in approximately 20 countries.

Adverse events will be collected in the eCRF for 90 days after dosing: up to Visit 8 (Day 91) for Sentinel Safety Cohort participants, and up to Visit 4 (Day 91) and from Visit 5 (Day 181) to Visit 8 (Day 271) for Main Cohort participants. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

For the Main Cohort, following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Sentinel Safety Cohort

The first 56 participants in the study will comprise the Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 6). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 6 Description of Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants

The ESDR for the Sentinel Safety Cohort will be conducted in 2 stages (as shown in Figure 1):

- An initial ESDR will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1 and 1b (a total of 14 participants) of the Sentinel Safety Cohort. During the initial ESDR, enrollment of participants will be paused. If the ESDR concludes that it is appropriate, then enrollment will be permitted to continue and sites will be informed in writing that dosing of the Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- A further ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Main Cohort will only be initiated if the ESDR of all of the Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile.

The safety data collected will be entered into eCRFs and reviewed. This review is based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDR:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters (if available)

For more details on the ESDR, see Section 4.1.3.

### 4.1.2 Main Cohort

The Main Cohort of the study will enroll approximately 3200 participants (Table 7). Dosing in the Main Cohort will be staggered, so that it starts with adult participants aged 18 years and

older, with no adolescent participants dosed in the Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156).

Participants in the Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention 6 months after Visit 1.

**Table 7 Description of Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (1600) | AZD7442 600 mg (1600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Planned analyses are discussed in Section 9.5.

### 4.1.3 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Sentinel Safety Cohort data, as discussed in Sections 4.1.1and 9.6.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

A dose ranging study will be conducted separately to the present study.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of

AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Main Cohort participants will all receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses. The assigned study intervention will be administered as 2 sequential IM injections, one injection for each mAb component, with the second injection administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions.

### 4.2.2 Rationale for Study Population

The Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1).

The adolescent population 12 to 17 years of age is included in this study to reflect the indication for AZD7442 (EVUSHELD), which includes the adolescent population despite not being included in the pivotal Phase 3 studies. Given the expected safety and PK profile of AZD5156, with no anticipated difference in the adolescent versus adult safety profile, the inclusion of the adolescent population allows for the generation of clinical data in this age group early in the AZD5156 clinical development plan. The adolescent population was approved for EVUSHELD based on the PK extrapolation.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of

AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ for the BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modeled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

### 4.3.3 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals at low risk of development of severe COVID-19 in order to maintain the double-blind in the Sentinel Safety Cohort and also better objectively assess the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the AZD7442 Phase I study (D8850C00001).

## 4.4 End-of-Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Negative rapid antigen test at Visit 1.
5 Weight ≥ 45 kg and ≤ 110 kg at screening.
6 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 Receipt of a COVID-19 antiviral within 3 months prior to Visit 1.

11 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

14 Active infection with hepatitis B or C.

15 Serum creatinine, AST, or ALT above 1.5 × ULN.

16 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

17 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

18 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

19 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

20 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

21 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Negative rapid antigen test at Visit 1.

4 Weight ≥ 40 kg at Visit 1 and Visit 5.

5 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have cancer (eg, active solid tumors and hematologic malignancies) except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

6 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no

acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

7 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), including those at Illness Visits, based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral within 3 months prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure, unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Details of these study interventions are presented in Table 8 and are described below.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material (the latter from a single production cell line which forms a Master Cell Bank and constitute the source of the commercial supply). In the Sentinel Safety Cohort, participants will receive only cell pools material. In the Main Cohort, participants may receive either cell pools material or clonal cell material.

The AZD1061 component of AZD5156 for the Sentinel Safety Cohort will initially be supplied from the AZD7442 clonal cell material. A more concentrated formulation of the clonal cell material for AZD1061 will be administered to participants in the Main Cohort. In the Main Cohort, participants may receive either the initially supplied AZD7442 material or the more concentrated material.

Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Sentinel Safety Cohort and the Main Cohort utilizing AZD3152 cell pool material and initially supplied AZD1061 material, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152. For AZD5156 in the Main Cohort utilizing AZD3152 clonal cell material and the more concentrated AZD1061 formulation, label-claim volume per vial is 2 mL for each component. For AZD7442 in the Main Cohort, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 IM injections, one injection for each component mAb, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895. This will ensure that all participants who only receive the first component of their assigned intervention will all received the same component (AZD1061).

**Table 8 Investigational Medicinal Products**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort and Main Cohort[a]** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort[b]** | **AZD7442 (AZD1061 + AZD8895) for Main Cohort** | **Placebo for Sentinel Safety Cohort** |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain either 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain either 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration** [c] | 2 IM injections (gluteal or thigh); 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections (thigh) of 2 mL each | 2 IM injections (thigh) of 3 mL each | 2 IM injections (gluteal or thigh): 3 mL and 2 mL |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product; w/v = weight per volume.

[a] In the Main Cohort, for the AZD3152 component, participants may receive cell pools material and for the AZD1061 component, participants may receive the initially supplied AZD7442 formulation (as shown in the column).

[b] In the Main Cohort, for the AZD3152 component, participants may receive clonal cell material and for the AZD1061 component, participants may receive the more concentrated formulation (as shown in the column).

[c] The second injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- The investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature-monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD5156 and AZD7442 for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (that is, the individual storage time limits are not additive). AZD5156 and AZD7442 do not contain

preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Main Cohort, participants will be randomized to receive 2 doses of AZD5156 or AZD7442 (1:1 ratio) at a 6-month interval. Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Sentinel Safety Cohort and Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist and administered by an unblinded administrator (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Personnel preparing and administering study intervention may be the same individual. Syringe masking will be required in order to maintain the blind.

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list and IRT/RTSM system
- The AstraZeneca supply chain department

- The unblinded AstraZeneca monitor or designee (if applicable)
- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives

during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy.

Table 9 lists the permitted and restricted medications for the Main Cohort.

**Table 9 Permitted, Restricted, and Prohibited Medications for the Main Cohort**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Intravenous immunoglobulin infusion for participants with common variable immunodeficiency | |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals should not be given within 3 months prior to Visit 1. Unless the participant develops COVID-19, at which point standard of care treatment is allowed, COVID-19 antivirals should not be given during the study until after the Day 29 assessments. |
| | EVUSHELD | EVUSHELD should not be given within 6 months prior to Visit 1. |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in the Sentinel Safety Cohort will receive a single dose of study intervention (AZD5156 or placebo). Participants in the Main Cohort will receive 2 doses of their assigned study intervention (AZD5156 or AZD7442), with the second dose administered approximately 6 months after the first dose, assuming the participant is still considered eligible for this second dose. For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 or Section 7.2.2 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules for Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.

- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any two Grade 3 or higher AEs, regardless of type, considered related to the study intervention by the Investigator or AstraZeneca.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Main Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the Main Cohort) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants

according to the time points specified in the SoA (Table 2 for the Sentinel Safety Cohort and Table 3 for Main Cohort). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, the Omicron variant BA.4/5, and the emerging dominant variant circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) to check for any COVID-19 symptoms experienced since the last contact and with reminders to monitor and report any COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week. For participants in the Main Cohort, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must be advised to contact the study site as soon as possible.

For participants in the Sentinel Cohort, if SARS-CoV-2 symptoms are reported, an Illness Visit is not required. The participant should be instructed to seek care via their usual healthcare provider.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Main Cohort will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 10).

**Table 10 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Main Cohort will be instructed to visit the study site for initiation of illness assessments and tested for SARS-CoV-2 using a local and central RT-PCR test and will perform home collection requirements as per the SoA (Table 4). Where supported, home visits may be substituted for the site visits.

Symptomatic participants will continue with the Illness Visits until a local RT-PCR result is available.

If the participant is confirmed to be positive by a local RT-PCR test, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the local RT-PCR test result is not evaluable, the participant will be instructed to continue with the Illness Visits for 14 days (as described in Table 4), including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits.

If the participant is confirmed to be negative for SARS-CoV-2 by a local RT-PCR test, the

participant will be instructed to stop all Illness Visit assessments and home laboratory kits and will continue with the main scheduled assessments (ie, Table 3).

A rapid antigen test may be performed locally only if a site does not have the capabilities to perform the RT-PCR test locally. Based on the test results, the decision to continue or stop Illness Visits should be made in the same manner as outlined above for RT-PCR laboratory test results.

Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 on a daily basis for up to 14 days in an Illness e-Diary. The Investigator (or designee) is required to review e-Diary data daily for each participant to ensure appropriate and on time completion.

The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.3).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of virus identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as

cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.

- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). On dosing days, vital signs will be performed predose and again approximately 10 to 15 minutes after both injections are given. The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

### 8.2.3 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort (see Section 1.3.1, Section 1.3.2, and Section 1.3.3).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 11.

**Table 11 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T/I (Main Cohort; screening only) |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal

For female participants in the Sentinel Safety Cohort aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (both cohorts), Visit 1 (both cohorts), and Visit 5 (Main Cohort only). The test must be negative before dosing. This is especially important for any female participants who have not reached menarche at enrollment into the study and whose child-bearing potential is expected to change during the study.

## 8.2.4 Other Safety Assessments

### 8.2.4.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source

document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.3.

#### 8.2.4.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Diameters of any redness/swelling will be recorded.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study days where study intervention is administered, the injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release. For the Sentinel Safety Cohort, injection site reactions will also be monitored on Days 3, 5, and 8.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 90 days following administration of study intervention. Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)

- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD5156 and AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Medically Attended Adverse Events

MAAEs will be collected according to the time points specified in the SoAs (Section 1.3).

MAAEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits will not be considered MAAEs.

### 8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to

the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs.

Where AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same

day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.10.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.11 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

#### 8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study

specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites

operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. For the Main Cohort, nasal lining fluid samples will be collected only for the first 1200 participants (approximately). Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$
- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Sentinel Safety Cohort and Table 3 for the Main Cohort). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being

screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs –Main Cohort only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by

next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort. Participants' data will be presented by the dosing regimen received.

## 9.1 Statistical Hypotheses

The primary objectives are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442.

In the Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442

with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 3256 participants will be randomized in the study. In the Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442.

A BSSR may be conducted prior to the primary analysis. The overall symptomatic COVID-19 event rate, as well as the data from external sources (eg, prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed. Full details will be in a BSSR plan.

The sample size in the Main Cohort is driven by the total number of events required to demonstrate the efficacy of AZD5156 versus AZD7442 in the prevention of symptomatic COVID-19. A minimum of 40 events will provide at least 90% to detect HR of 0.3, or a 70% reduction in hazard. Under the assumption that the event rate will be approximately 3.2% AAR in the AZD7442 arm, HR of 0.30 (70% efficacy), significance level of $\alpha$=0.05, and 10% attrition. A target sample of approximately 3200 participants has been selected to reach the required number of events assuming participants were observed for 8 months or more. Assumptions are based on data from prior studies with AZD7442 and reported estimates of the AAR among those with immunocompromising conditions (Kelly et al 2022).

A sample size of approximately 1200 participants in the Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from

prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

The main cohort sample size of 3200 participants provides a safety and PK database of over 1600 participants who will receive AZD5156 compared with 1600 participants receiving a US EUA granted and EU MAA approved active comparator, AZD7442.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Anti-drug antibody analysis set | All participants in the FAS with baseline and postdose anti-drug antibody results. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |
| Immunobridging analysis set | Participants in the FAS who have a baseline and post intervention Day 29 antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints to be evaluated in the Main Cohort.

### 9.4.1 General Considerations

This study is designed to evaluate the immunobridging, efficacy, and safety of AZD5156 compared with AZD7442. The primary endpoint is a noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received. Methods for controlling multiplicity across endpoints will be presented separately in the SAP for the immunobridging and efficacy analyses.

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary and secondary analyses.

### 9.4.2 Efficacy

The symptomatic COVID-19 efficacy endpoint is time in days from IMP administrations until a participant develops symptomatic COVID-19 at any time up to Visit 9 (12 months). Positive cases require a central RT-PCR test and meet the qualifying symptoms satisfying the modified WHO definition of symptomatic COVID-19 (see Section 8.1.2).

The symptomatic COVID-19 efficacy endpoint will be evaluated with a Cox proportional hazard model, which includes study intervention and stratification factors as covariates to assess intervention (ie, HR) between AZD5156 and AZD7442. The estimated HR with corresponding 95% CI and 2-sided p-value for testing the null hypothesis from the model will be reported. Model assumptions will be evaluated with additional sensitivity analyses, including a review of the proportional hazards assumption. If this assumption is violated, an extended Cox model may be implemented, with details outlined in the SAP.

Participants who become unblinded to treatment assignment and/or take other noninvestigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will be censored at the date of unblinding or receipt of the first dose of COVID-19 preventive product. Participants may receive additional treatments as per the standard of care to manage symptoms or prevent progression to severe COVID-19. These participants would have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and will be included in the analysis. Participants that withdraw early from the study and deaths unrelated to COVID-19 will be censored at the earliest date of such events.

Other efficacy secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 and Day 361 where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis.

- Incidence of post-treatment symptomatic COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will also be evaluated. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Anti-drug Antibody Variables

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total number of participants with negative ADA assay response at all times
- Total number of participants with positive ADA assay response at any time
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response

at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels

- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay
- Titer values
- Titer category

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following initial dosing with AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

## 9.5 Planned Analyses

No interim analyses are planned. The primary analyses will occur after the first 1200 participants (approximately) in the Main Cohort have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end-of-study visit. An evaluation of efficacy may be conducted by a separate unblinded team should 40 or more participants with symptomatic COVID-19 be

observed prior to the final analysis. The study will maintain a double-blind period until the primary analysis. To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in a Study Integrity Plan; the study team will remain blinded. Participant-level unblinding information will be kept strictly confidential, and the rationale for any unblinding will be documented. The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis, including efficacy, will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee - Sentinel Safety Cohort

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDR of the Sentinel Safety Cohort, as discussed in Section 4.1.3.

## 9.7 Data Safety Monitoring Board – Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. This review will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of the first 80 adult participants (approximately 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrolment of adolescents into the Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

## C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

(a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

(b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 13, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 13 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

| | | |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

| | | |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care

# Appendix F Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

### CSP Version 1.0 / Local CSP 1 United States [30 November 2022]

This modification is considered to be substantial due to the number of substantial changes introduced, as detailed below.

### Overall Rationale for the Modification:

The addition of efficacy as a secondary endpoint to provide clinical efficacy to support the use of AZD5156 in the pre-exposure prophylaxis setting. This required an increase in the sample size from 1200 participants in the main cohort to 3200 participants in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156. To accommodate this, the Day 181 re-dosing will change so that participants receive the same IMP as was originally received.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3 Schedule of Activities | For both cohorts, the collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 1.3 Schedule of Activities | For both cohorts, MAAEs will be collected throughout the study | To ensure that MAAEs are identified and collected |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Electrocardiogram added at screening | This was a Regulatory Authority request, included to confirm the lack of any significant cardiac findings in all participants and to assure the healthy status of the participants in the Sentinel Safety Group |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Added assessment of troponin | To increase cardiac safety monitoring |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1 | To align with internal guidance for WOCBP |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Laboratory safety testing added at Visit 1 | To obtain baseline values |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | The weekly assessment for monitoring of safety and COVID-19 qualifying symptoms has been removed for the Sentinel Safety Cohort | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | An additional assessment of injection site reactions has been added at Day 8 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | A screening period has been added for the Main Cohort. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | An additional visit has been added to the schedule of activities, at Day 451; this visit will be completed by telephone | To increase the safety collection time to five half-lives from the initial dose (15 months total). |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Electrocardiogram has been added as a screening assessment for the Main Cohort | Added for consistency with screening for the Sentinel Safety Cohort |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | Additional assessments of injection site reactions have been added at Days 8 and 189 | This extra check has been added 1 week after dosing to check for severe reactions |
| 1.3.3 Screening, Treatment, and Follow-up Activities –Main Cohort Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 1.3.3 Treatment and Follow-up Activities –Main Cohort Participants | Added footnote to state that for the Main Cohort, nasal lining fluid samples will be collected only for approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Assessments of AEs, SAEs, MAAEs, and AESIs has been added | This assessment has been added in case events occur outside of the AE windows for the concurrent Main Cohort assessments |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Set up of e Diary and training has been added | Clarification |
| 3 OBJECTIVES AND ENDPOINTS | Primary safety endpoint includes occurrence of AEs collected through 90 days after IMP administration (was previously to Day 29) | For both cohorts, the collection period for AEs has been increased from 29 to 90 days after each dose of study intervention |
| 3 OBJECTIVES AND ENDPOINTS | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |
| 3 OBJECTIVES AND ENDPOINTS | Additional details added to the secondary endpoint related to efficacy | With the increased sample size the secondary endpoint, symptomatic COVID-19, is expected to be appropriately powered to test efficacy and support the use of AZD5156 in the pre-exposure prophylaxis setting |
| 4.1 Overall Design | The concept of the study having Parts A and B has been eliminated, and all references to a specific Part B of the study have been deleted.<br>This change has been implemented throughout the protocol amendment, and so a complete list of protocol sections affected by this change is not provided. | As there is no longer any switching of study intervention during the Main Cohort, there is no longer the need to make this distinction |
| 4.1 Overall Design | For the Main Cohorts, the duration of the study has been increased from approximately 12 to 15 months | To increase the safety collection time to five half-lives from the initial dose (15 months total). |
| 4.1 Overall Design | The number of participants in the Main Cohort has increased from 1200 to 3200 | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | The number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design | Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Added details of second ESDR review | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |
| 4.1 Overall Design | Noted that dosing in the Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants have been reviewed | This was a Regulatory Authority request, such that data from a minimum number of adult subjects in the main group (beyond Day 8) are reviewed and deemed supportive prior to initiating enrollment of adolescent subjects |
| 4.1 Overall Design | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 4.1 Overall Design | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 4.1 Overall Design | MAAEs have been added as a safety endpoint | To ensure that MAAEs are identified and collected |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.1 Sentinel Safety Cohort | The ratio of participants receiving AZD5156 or placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1.3 Safety Review | Section updated | Specific details of the separate ESDR and DSMB reviews have been added |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion #1 added to ensure participants are healthy | Added for clarity |
| 5.1.1 Inclusion Criteria (Sentinel) | The original inclusion #3 has been deleted | Duplication with the original inclusion #6 |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.2 Exclusion Criteria (Sentinel) | Exclusion #10 added (Receipt of a COVID-19 antiviral within 3 months prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #11, window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 5.1.2 Exclusion Criteria (Sentinel) | For exclusion #15, hemoglobin, white blood cell count, and platelet count below lower limit of normal are no longer exclusionary, and for creatinine, AST, and ALT the exclusionary level has been increased to 1.5 × ULN | This has been updated for consistency with protocols currently being developed for AZD5156 |
| 5.2.1 Inclusion Criteria (Main) | The original inclusion #3 has been deleted | Duplication with the original inclusion #8 |
| 5.2.2 Exclusion Criteria (Main) | For exclusion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.1.2 Exclusion Criteria (Main) | Exclusion #11 added (Receipt of a COVID-19 antiviral within 3 months prior to Visit 1) | For consistency with addition of COVID-19 antivirals to the list of restricted medications |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2.2 Exclusion Criteria (Main) | For exclusion #12, window for COVID-19 has been reduced from 6 to 3 months | For broader inclusivity |
| 6.1 Study Intervention(s) Administered | The ratio of participants receiving AZD5156 or placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.1 Study Intervention(s) Administered | The placebo injections (as detailed in Table 8) have been amended from 2 × 2 mL to 3 mL plus 2 mL | The volumes have been adjusted to match those used for the administration of AZD5156 in the Sentinel Safety Cohort |
| 6.3.1 Randomization | The ratio of participants receiving AZD5156 or placebo has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 6.5 Concomitant Medication | Noted that, for the Sentinel Safety Cohort, the only permitted concomitant medications are contraceptives or hormone replacement therapy. | Clarification |
| 7.1 Discontinuation of Study Intervention | For the second dose administered for the Main Cohort (Day 181) participants will receive the same study intervention that they were randomized to for Day 1 dosing | Participants randomized to AZD7442 for their first dose of study intervention will no longer be switched to AZD5156 for their second dose |
| 7.2 Participant Withdrawal from the Study | Noted that if any of the stopping criteria are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart | This was a Regulatory Authority request |
| 7.2.1 Stopping Rules for Sentinel Safety Cohort | An additional stopping criteria has been added: two or more severe adverse drug reactions, regardless of type. | This was a Regulatory Authority request |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.2.2 Stopping Rules for Main Cohort | Amended the text on temporary hold, noting that the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants | This was a Regulatory Authority request |
| 8.2.3 Clinical Safety Laboratory Assessments | Added assessment of troponin at screening only | To increase cardiac safety monitoring |
| 8.3.1 Time Period and Frequency for Collecting AE and SAE Information | The collection period for AEs has been increased from 29 to 90 days after each dose of study intervention | To align with global regulatory requirements for AE follow-up |
| 8.3.5 Medically Attended Adverse Events | New section | To clarify how these will be captured |
| 8.3.11.4 Drug Misuse | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 8.5.1 Pharmacokinetics | Noted that for the Main Cohort, nasal lining fluid samples will be collected only for the approximately the first 1200 participants | Introduced to reduce the burden of nasal sampling |
| 9.2 Sample Size Determination | The number of participants in the Main Cohort has increased from 1200 to 3200, and text has been added to discuss sample size in relation to the efficacy analysis, immunobridging analysis, and safety/PK | The addition of efficacy as a secondary endpoint requires an increase in the sample size in order to acquire 40 events to demonstrate efficacy between AZD7442 and AZD5156 |
| 9.2 Sample Size Determination | The number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 9.2 Sample Size Determination | Text added to discuss how a BSSR would be conducted | A BSSR may be conducted prior to the efficacy analysis |
| 9.3 Populations for Analyses | Immunobridging analysis set added | Analysis set to be used for immunobridging analysis |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.4.2 Efficacy | Section updated and expanded to include details of symptomatic COVID-19 efficacy endpoint | Section updated to reflect efficacy secondary endpoint |
| 9.6 Safety Review Committee - Sentinel Safety Cohort | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 9.7 Data Safety Monitoring Board – Main Cohort | New section | Added to ensure external review of safety and integrity of the Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities | For both cohorts, 'Month' has been added to the Schedule of Activities | Added for clarity |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Added details of the timing of postdose vital signs assessments to footnote (a) | This information was omitted from this footnote in the original protocol |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | For footnote (a), the reference to daily oral temperature as part of COVID-19 monitoring has been removed | This assessment is related to qualification for the Illness Visits, which are only applicable for Main Cohort participants |
| 1.3.2 Treatment and Follow-up Activities – Sentinel Safety Cohort Participants | Footnote (d) added to clarify that the results from the NP swab for SARS-CoV-2 RT-PCR (central laboratory) are not needed prior to dosing | Clarification |
| 1.3.3 Treatment and Follow-up Activities –Main Cohort Participants | The timing of the Visit 1 assessment has been changed from predose to prior to randomization | Pregnancy is an exclusion criterion, and eligibility should be confirmed before randomization. |
| 1.3.3 Treatment and Follow-up Activities – Main Cohort Participants | On Day 181, several assessments are now indicated as being required predose | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Treatment and Follow-up Activities – Main Cohort Participants | Clarified details of the timing of postdose vital signs assessments to footnote (b), and noted that any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes | The information about abnormal vital signs was omitted from this footnote in the original protocol |
| 1.3.3 Treatment and Follow-up Activities – Main Cohort Participants | Footnote (e) has been added to the Day 181 assessment of the NP swab for SARS-CoV-2 RT-PCR (central laboratory) | The Day 181 results are not required prior to dosing |
| 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms | Footnote (d) has been updated and expanded | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 2.1 Study Rationale | Noted that AZD5156 is being developed to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve | Clarification |
| 2.1 Study Rationale | Added that the study will be used as a demonstration of efficacy of AZD5156 compared to EVUSHELD | Update to reflect the secondary endpoint related to efficacy |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | The number of confirmed cases of COVID-19 has been updated | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term ‘currently circulating Omicron variants’ has been replaced with ‘past dominant variants’ | This information has been brought up to date |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The term ‘ADE disease’ has been replaced with ‘ADE of infection’ | The revised wording more accurately describes the effect |
| 2.2.2 Combination Products - AZD5156 and AZD7442 | The list of Omicron variants where AZD5156 has superior nonclinical viral neutralization data compared with AZD7442 has been expanded | This information has been brought up to date |
| 2.3.1 Risk Assessment | The term ‘ADE disease’ has been replaced with ‘ADE of infection’ | The revised wording more accurately describes the effect |
| 2.3.1 Risk Assessment | Added that cardiovascular and thromboembolic events will continue to be monitored in the AZD5156 studies | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | The numbers of sites and countries have been increased | This is a reflection of the increased sample size |
| 4.1.1 Sentinel Safety Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.1.1 Sentinel Safety Cohort | Noted that the pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met. | Clarification |
| 4.1.2 Main Cohort | Some details have been removed from this section | The text removed was duplicated from earlier in the same main section (Section 4.1) |
| 4.2 Scientific Rationale for Study Design | Noted that a dose ranging study will be conducted separately to the present study | Clarifies why the present study only includes Phase I/III components |
| 4.2.2 Rationale for Study Population | Text has been added to justify the inclusion of the pediatric population (12 to 17 years of age) | Additional details added to give a more comprehensive rationale for the study population |
| 4.3.1 Justification for AZD5156 Dose | Expanded list of variants where AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{80}$ | This information has been brought up to date |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 5.4 Screen Failures | Criteria for rescreening has been updated | To allow broader inclusion of participants |
| 6.1 Study Intervention(s) Administered | Noted that all participants who only receive then first component of their assigned intervention will all received the same component (AZD1061) | Rationale for order of injections |
| 6.1 Study Intervention(s) Administered | Wording around sources of IMP components has been updated | Updated to reflect current information |
| 6.2 Preparation/Handling/ Storage/Accountability | Extra information has been added regarding the storage of IMP | Wording added to provide more comprehensive details of IMP storage |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.3.2 Blinding | Removed text about investigator being available in case of emergency | In this context, the statement was not appropriate |
| 6.3.2 Blinding | Added extra information regarding personnel preparing and administering study intervention | Clarification |
| 6.5 Concomitant Therapy | Added that intravenous immunoglobulin infusion for participants with common variable immunodeficiency is a permitted concomitant medication | Clarification |
| 6.5 Concomitant Therapy | Added COVID-19 antivirals and EVUSHELD to the restricted section of the table | To ensure the correct patient population is enrolled |
| 7.2.2 Stopping Rules for Main Cohort | Replaced some of the existing text with text about the DSMB | Updated to reflect the addition of a DSMB for the Main Cohort |
| 8 STUDY ASSESSMENTS AND PROCEDURES | Expanded text on repeat or unscheduled samples | Updated as this may include results from external laboratories where participants have tested positive for COVID-19 but are not able to attend for an Illness Visit |
| 8.1.2 Participant reported COVID--19 Symptoms | Minor edits made throughout the section | Updated for clarity |
| 8.1.3 Illness Visits | The wording in this section has been reworked | This change has been made for clarity and for alignment around COVID-19 testing requirements for Illness Visits |
| 8.2.1 Physical Examinations | Removed text regarding who will perform the assessment | Clarification |
| 8.2.2 Vital Signs | Added details of the timing of postdose vital signs assessments | This information was omitted from this section of the original protocol |
| 8.2.3 Clinical Safety Laboratory Assessments | Details of timing of pregnancy tests updates | The Sentinel Safety Cohort now has a test at Visit 1 |
| 8.2.4.1 Immediate Adverse Events | Noted that management of anaphylaxis and hypersensitivity should occur in accordance with current standard of care and clinical guidelines | Clarification |
| 8.2.4.2 Injection Site Reactions | Noted that diameters of any redness/swelling will be recorded | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.3.11.1 Timelines | Updated wording for SAE associated with events of medication error to also include drug abuse and misuse | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| 9.3 Populations for Analyses | Added that the safety analysis set will include participants from the FAS but report participants according to the actual treatment received (regardless of assigned treatment) | Clarification |
| 9.4.1 General Considerations | Text about controlling multiplicity added | Section updated to reflect the change in secondary endpoint |
| 9.4.2 Efficacy | Subheadings related to primary, secondary, and exploratory endpoints have been removed and the corresponding text redistributed to more appropriate parts of the document | To improve the readability of the section |
| 9.5 Planned Analyses | Added details of primary analysis after approximately 1200 participants and that study team will remain blinded during primary analysis | Clarifications |
| 9.6 Safety Review Committee - Sentinel Safety Cohort | Clarified that this will now only apply to the Sentinel Safety Cohort | Required due to removal of the concept of study having Parts A and B |
| A 6 Data Quality Assurance | Statement regarding QTLs added | Added to bring the protocol in line with current AstraZeneca protocol standards |
| A 6 Data Quality Assurance | Wording regarding retention of records and documents amended | Updated to bring the protocol in line with current AstraZeneca protocol standards |
| A 8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# SIGNATURE PAGE

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| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | AZD5156 |
| Study Code | D7000C00001 |
| Version | 1.0 (Local CSP 1 Germany) |
| Date | 14Feb2023 |

# A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): EudraCT Number 2022-002378-95**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

Amendment Number: Local CSP 1 Germany

Study Intervention: AZD5156, a combination product of 2 monoclonal antibodies (AZD1061 [cilgavimab] and AZD3152); AZD7442 (EVUSHELD™), the active comparator; and placebo (0.9% sodium chloride for injection)

Study Phase: I/III

**Title:** A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Acronym:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies)

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Version 1.0 / Local CSP 1 Germany | 14-Feb-2023 |
| CSP Version 1.0 | 26-Sep-2022 |

### CSP Version 1.0 / Local CSP 1 Germany [14 February 2023]

This modification is considered to be substantial due to the introduction of additional safety assessments, as detailed below.

### Overall Rationale for the Modification:

The protocol has been amended to enhance the safety assessments of the Sentinel Safety Cohort and the Main Cohort, as well as add more details around contraception requirements and woman of childbearing definition, at the request of Paul-Ehrlich-Institut.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities | A screening period has been added for the Part A Main Cohort | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants | Added assessment of follicle stimulating hormone at screening | Required for eligibility criteria |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Pregnancy test added at Visit 1 predose; noted that the test must return a negative result before dosing | To align with internal guidance for WOCBP |
| 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants | Additional Safety laboratory investigations have been included at Day 1 and Day 15 (in addition to Day 8, Day 29, and Early Discontinuation Visit) | To increase safety monitoring of participants, meet regulatory requirements, and to facilitate the ESDR of the Day 15 data. |
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | A screening period has been added. Accordingly, some assessments previously scheduled for Visit 1 have been moved to screening. | This change has been made to ensure there is an opportunity to assess and screen any vulnerable participants. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | An additional visit has been added at Day 15 for the first 80 adult participants in the Part A Main Cohort | The safety review prior to dosing adolescents required 2 weeks of safety data |
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | Weight was included in Visit 5, pre dose. | To verify eligibility based on weight at Visit 5 before the second dose is administered |
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | Added urine pregnancy test at screening and noted that the urine pregnancy test on the Visit 5 will be pre dose. | Clarified that pregnancy tests on Visit 5 Day 181 must be performed prior to dosing |
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants<br>8.2.3 Clinical Safety Laboratory Assessments | Clarified that negative pregnancy test results before each dose are especially important for any female participants who have not reached menarche at enrollment | The child-bearing potential of these participants may change during the study |
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | Added assessment of follicle stimulating hormone at screening | Required for eligibility criteria, according to internal guidance for WOCBP |
| 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | The table footnote has been expanded to note that the ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | The number of participants for Part A Sentinel Safety Cohort has been increased to 56, as the number of participants receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.1 Overall Design<br>4.1.1 Part A Sentinel Safety Cohort<br>6.1 Study Intervention(s) Administered<br>6.3.1 Randomization | The ratio of participants receiving AZD5156 and placebo in Part A Sentinel Safety Cohort has been amended from 10:1 to 5:2 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design | Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts | This was a Regulatory Authority request, to allow evaluation of safety and tolerability of a subset of participants before enrolling subsequent participants |
| 4.1 Overall Design | The initial ESDR has been extended to encompass Visit 5 (Day 15) as well as Visit 4 (Day 8). Noted that enrollment of the Part A Main Cohort will be initiated if the safety review at Day 15 concludes that the safety profile is acceptable (previously stated only that it would be initiated when the review concluded it was appropriate to do so) | This was a Regulatory Authority request, to increase the minimum data requirements to support initiation of the Main Cohort |
| 4.1 Overall Design | Noted that dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data have been reviewed for at least 40 adult participants in the Main Cohort | This was a Regulatory Authority request, such that data from a minimum number of adult participants in the Main Cohort (beyond Day 8) are reviewed and deemed supportive before enrolling adolescent participants |
| 4.1 Overall Design<br>6.1 Study Intervention(s) Administered | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) | To limit the injection volume into the muscle to reduce risk of local site reactions |
| 4.1.1 Part A Sentinel Safety Cohort | Added details of subcohorts and the ESDRs | Incorporated due to the division of the Sentinel Safety Cohort into subcohorts |
| 4.1.4 Safety Review | Noted that an independent DSMB has been added to the study to provide oversight to ensure the safe and ethical conduct of the Part A and Part B Main Cohort | Specific details of the separate ESDR and DSMB reviews have been added |
| 4.2.1 Rationale for Administration Site | Noted that the second component injection will be administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions | To further clarify rationale for the administration site |
| 5.1.1 Inclusion Criteria (Sentinel) | Inclusion criterion #1 added to ensure participants are healthy | Added for clarity |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1.2 Exclusion Criteria (Sentinel)<br>5.2.2 Exclusion Criteria (Main Cohort)<br>5.3.2 Exclusion Criteria (Part B) | For exclusion criterion #1, more details around contraception requirements have been added | This section has been added to bring the protocol in line with current AstraZeneca protocol standards, and to comply with a Regulatory Authority request |
| 5.3.1 Inclusion Criteria (Part B) | The inclusion criterion of weight ≥ 40 kg will now also be assessed at Visit 5 in addition to Visit 1 | This was a Regulatory Authority request, to verify eligibility based on weight at Visit 5 before the second dose is administered. |
| 8.2.4 Clinical Safety Laboratory Assessments | Noted that for some female participants FSH will be included as part of the laboratory assessments at screening | This has been added to assist with making a decision regarding whether a female participant is postmenopausal, as per the exclusion criteria |
| 9.7 Data Safety Monitoring Board – Part A and Part B Main Cohort | New section | Added to ensure external review of safety and integrity of the Part A and Part B Main Cohort of the study |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | The synopsis has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.2 Schema | The schema has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 1.3.1 Screening Activities – Sentinel Safety Cohort Participants<br>1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants<br>1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants | Noted that pregnancy test will be performed at a local laboratory | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | The synopsis has been updated to reflect the changes introduced in this amendment | Updated for consistency with other parts of the protocol |
| 4.1 Overall Design<br>9.2 Sample Size Determination | The overall number of participants has been increased from 1244 to 1256, as the number of participants in the Sentinel Safety Cohort receiving placebo has been increased from 4 to 16 | This was a Regulatory Authority request, to increase the number of participants who receive placebo, to allow evaluation of safety and tolerability of a subset of participants before imitating the Main Cohort |
| 4.3.3 Justification for Placebo | New section | This section has been added to bring the protocol in line with current AstraZeneca protocol standards |
| 6.3.2 Blinding | Added the DSMB as having access to the randomization list during the study | Clarification |
| 8.2.3 Clinical Safety Laboratory Assessments | Clarified that where pregnancy tests are performed on a dosing day, the test must be performed on the same day as the dose is administered, prior to dosing. | Clarification |
| 8.3.8 Reporting of Serious Adverse Events | Minor change to wording of statement about reporting of SAEs | Amended to bring the protocol in line with current AstraZeneca protocol standards |
| A8 Study and Site Start and Closure | Added reference to DSMB | If the study is prematurely terminated or suspended, the Sponsor needs to inform the DSMB |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Antidrug antibody |
| ADE | Antibody dependent enhanced |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve at the last measured time point |
| C1q | Complement component 1q |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| $C_{max}$ | Maximum concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DBL | Database lock |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| ESDR | Early safety data review |
| EU | European Union |
| EUA | Emergency Use Authorization |
| FAAN | Food Allergy and Anaphylaxis Network |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |

| Abbreviation or special term | Explanation |
|---|---|
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HL | Hy's law |
| $IC_{90}$ | Concentration required for 90% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| Ig | Immunoglobulin |
| IL-D | Illness Day |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIAID | National Institute of Allergy and Infectious Disease |
| NIMP | Non-investigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| QTL | Quality tolerance limits |
| RBD | Receptor-binding domain |
| RNA | Ribonucleic acid |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SoA | Schedule of activities |
| $SpO_2$ | Oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{½}$ | Terminal half-life |

| Abbreviation or special term | Explanation |
|---|---|
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| $t_{max}$ | Time to maximum serum concentration |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase I/III Randomized, Double-blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

**Rationale:**

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab]), approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## Objectives and Endpoints – Part A

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score $\geq 4$)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

## Objectives and Endpoints – Part B

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol. Exploratory endpoints may be reported separately from the CSR.

**Overall Design**

D7000C00001 is a Phase I/III study that will be conducted in approximately 1256 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). Early safety data reviews will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Part A Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable. Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Part A Main Cohort until Day 15 safety data for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues.

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when

checked at Visit 5 (Day 181). For participants who take part in Part B, the follow-up will be 6 months from the open-label administration of AZD5156, and the total duration of involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections in the thigh, one injection for each mAb component, with the second injection administered in the contralateral side. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported. The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B Visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

**Disclosure Statement**:

This is a parallel group, safety and immunogenicity study, with Part A comprising a Sentinel Safety Cohort and a modified double-blinded Main Cohort (ie, with an unblinded study intervention administrator independent of the safety evaluation and other trial evaluations used at each trial site; the participant and Investigator will be blinded). Participants from Part A Main Cohort will continue to the single-arm, open-label Part B, where they will receive a dose of AZD5156, approximately 6 months after their first study intervention administration. Participants who join Part B of the study will remain blinded to the study intervention received at Visit 1 in Part A.

**Number of Participants:**

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 16 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

**Intervention Groups and Duration:**

Part A: Sentinel Safety Cohort: single dose of AZD5156 600 mg IM or placebo IM.

Part A: Main Cohort: single dose of AZD5156 600 mg IM or AZD7442 600 mg IM.

Part B: single open-label dose of AZD5156 600 mg IM.

The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

**Safety Review Committee:**

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Part A Sentinel Safety Cohort as follows: after Visit 4 (Day 8) and Visit 5 (Day 15) of the first 2 subcohorts (1a and 1b), prior to the initiation of the final 2 subcohorts (2a and 2b), and subsequently after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 subcohorts, prior to enrollment of the Part A Main Cohort.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data from the Part A and Part B Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Part A Main Cohort.

**Statistical Methods**

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated.

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort

participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit.

*Primary Objectives*

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3.

Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. The 2-sided 95% CI for the ratio of GMTs will be calculated using log-transformed concentrations.

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

*Secondary Objectives*

<u>SARS-CoV-2 nAb Response</u>

The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will be evaluated in Part A.

<u>Efficacy Endpoints</u>

Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be

excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

Characterization of PK

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time. Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout. Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

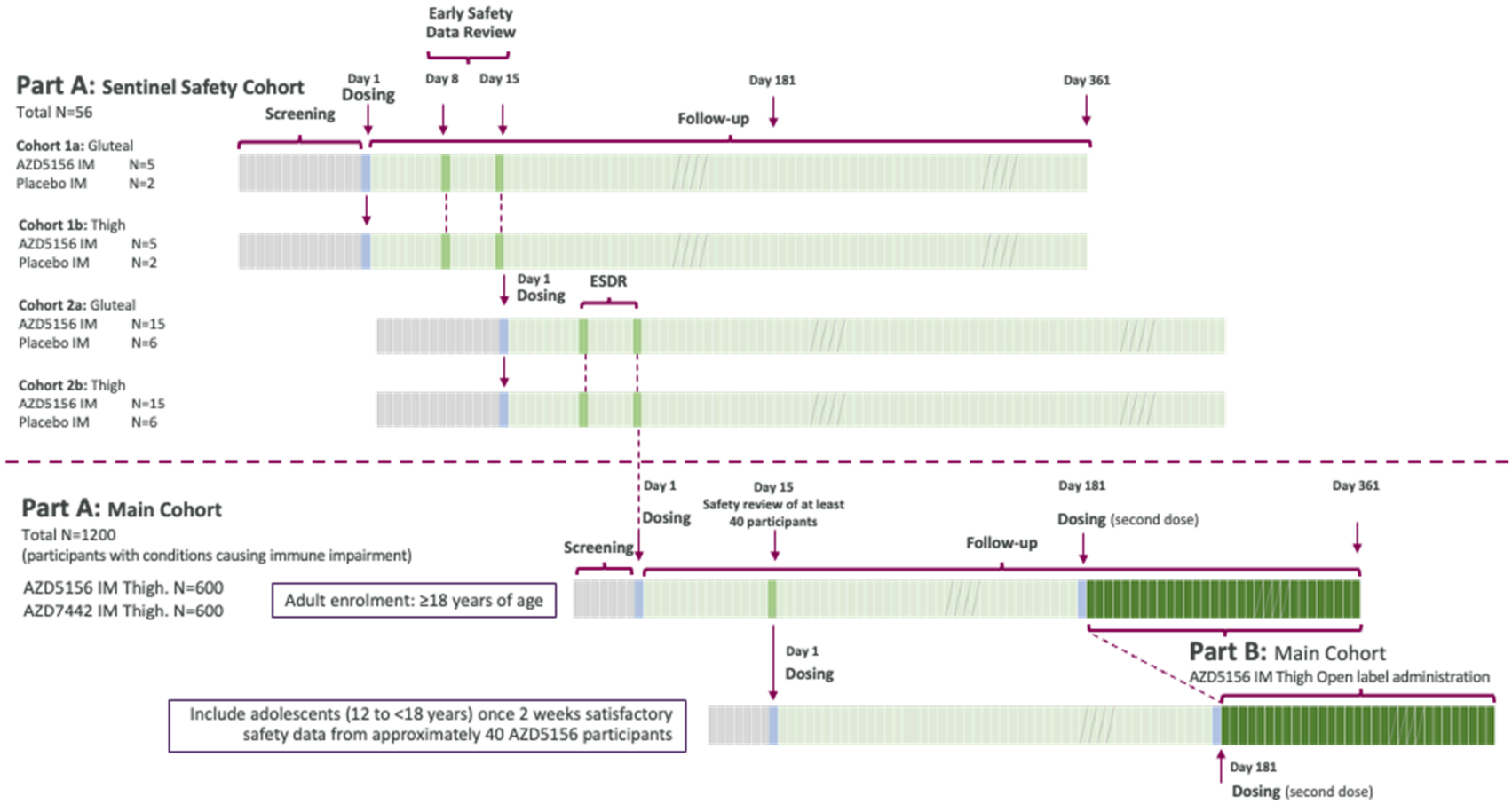
Evaluation of ADA

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




ESDR = early safety data review; IM = intramuscular; N = number of participants.
Note: An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of the Part A Sentinel Safety Cohort (data up to Day 15), prior to the initiation of the final 2 subcohorts (2a and 2b), and then prior to enrollment of the Main Cohort.
Note: Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Main Cohort until Day 15 safety data for at least 80 adult Main Cohort participants (which will include approximately 40 participants who have received AZD5156) have been reviewed.

## 1.3 Schedule of Activities

For Part A Sentinel Safety Cohort participants, the study will consist of 2 periods:

- A screening period of up to 14 days (Day -14 through Day -1) (Table 1).
- A treatment and follow-up period lasting 12 months after the administration of study intervention (Table 2).

For Part A Main Cohort participants, there will be a screening period of up to 8 days (Day -7 through Day 1) and a treatment and follow-up period lasting 12 months (inclusive of Part B) after administration of study intervention at Visit 1 (Table 3).

All active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will be considered for inclusion in the open-label Part B after approximately 6 months (Table 3).

For Part A Main Cohort and Part B participants with qualifying symptoms of COVID-19, additional Illness Visits should be incorporated in the schedule (Table 4) as described in Section 8.1.3.

### 1.3.1 Screening Activities – Sentinel Safety Cohort Participants

**Table 1 Schedule of Activities (Screening Period) - Sentinel Safety Cohort**

| Procedure | Screening Visit (Day -14 to Day -1) |
|---|---|
| Written informed consent | X |
| Verify eligibility criteria | X |
| Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) | X |
| Full physical examination, including height and weight | X |
| Vital signs | X |
| Serum chemistry, hematology, coagulation (local laboratory) [a] | X |
| Urine pregnancy test [b] (WOCBP only, local laboratory) | X |
| Concomitant medications | X |
| SAEs | X |

[a] Including follicle stimulating hormone, if applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[b] Pregnancy test must be negative at screening.
SAE = serious adverse event; WOCBP = women of childbearing potential.

### 1.3.2 Treatment and Follow-up Activities – Part A: Sentinel Safety Cohort Participants

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Verify eligibility criteria | X (predose) | | | | | | | | | | | |
| Randomization | X (predose) | | | | | | | | | | | |
| Targeted physical examination based on medical history | X (predose) | | | | | | | | | | | |
| Vital signs [a] | X (predose) | | | | | | | | | | | X |
| Urine pregnancy test (WOCBP only, local laboratory) [b] | X (predose) | | | | | | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [c] | X (predose) | | | | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | X (predose) | | | | | | | | | | | |
| Serum chemistry, hematology, coagulation (local laboratory) | X (predose) | | | X | X | X | | | | | | X |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| **Procedure** | **Treatment and Follow-up Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Weekly telephone/email/text contacts – monitoring for safety and COVID-19 qualifying symptoms [d] | X ← → | | | | | | | | | | | |
| Assessment of AEs | X | | | | | | | | | | | |
| Assessment of SAEs and AESIs | X (ongoing observation and questioning) | | | | | | | | | | | |
| Concomitant medications | X (ongoing observation and questioning) | | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | X (predose) | | | | | X | | X | X | | X | X |
| PK serum sample [e] | X (predose) | X | X | X | X | X | X | X | X | X | X | X |
| PK nasal lining fluid sample | X (predose) | X | X | X | | X | | X | X | | | |
| ADA serum sample | X (predose) | | | | | X | | X | X | X | X | |
| SARS-CoV-2 neutralizing antibody serum sample | X (predose) | X | X | X | X | X | X | X | X | X | X | |
| Exploratory analysis serum sample | X (predose) | | | X | | X | X | X | X | X | X | |
| **Study intervention administration** | X | | | | | | | | | | | |

**Table 2 Schedule of Activities (Treatment and Follow-up Period) – Part A: Sentinel Safety Cohort**

| Procedure | Treatment and Follow-up Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **EDV** |
| **Day** | **1** | **3** | **5** | **8** | **15** | **29** | **58** | **91** | **181** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **+ 1** | **+ 1** | **+ 1** | **± 3** | **+ 3** | **± 5** | **± 5** | **± 10** | **± 10** | **± 14** | **NA** |
| Injection site reaction monitoring (local reactogenicity) [f] | X | | | | | | | | | | | |
| Immediate AEs [g] | X | | | | | | | | | | | |

[a] Any abnormal vital signs must be repeated after the participant has been at rest for at least five minutes. As part of COVID-19 monitoring daily oral temperature measurements during in-house stay and at every outpatient visit will be implemented.

[b] Sample urine test must return a negative result before dosing.

[c] Sites will be provided with rapid antigen tests.

[d] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.

[e] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.

[f] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.

[g] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

ADA = antidrug antibodies; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; NP = nasopharyngeal; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = woman of childbearing potential.

### 1.3.3 Treatment and Follow-up Activities – Part A: Main Cohort and Part B Participants

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b** | **3** | **4** | **5** | **6[a]** | **7[a]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Written informed consent | X | | | | | | | | | | | |
| Informed assent for pediatric participants | X | | | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | X | | | | | |
| Randomization | | X (predose) | | | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | | | |
| Full physical examination, including height and weight | X | | | | | | Weight only (predose) | | | | | X |
| Vital signs | | X [b] | | | | | X | | | | | |
| Urine pregnancy test (WOCBP only, local laboratory) [c] | X | X (predose) | | | | | X (predose) | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [d] | | X (predose) | | | | | X | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) | | X [e] (predose) | | | | | X | | | | | |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| **Procedure** | | **Treatment and Follow-up Period** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b** | **3** | **4** | **5** | **6[a]** | **7[a]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Follicle stimulating hormone [g] | X | | | | | | | | | | | |
| Weekly telephone/email/text contacts- monitoring for safety and COVID-19 qualifying symptoms [h] | | X ← → | | | | | | | | | | |
| Assessment of AEs | | X | | | | | X | | | | | |
| Assessment of SAEs, and AESIs | X (SAE) | X (ongoing observation and questioning) | | | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | | X | X | X | | | | X | X |
| PK serum sample [i] | | X (predose) | | | X | X | X (predose) | X | X | X | X | X |
| PK nasal lining fluid sample | | X (predose) | | | X | X | | | | | | |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| SARS-CoV-2 nAb serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |

**Table 3 Schedule of Activities (Treatment and Follow-up Period) – Part A: Main Cohort and Part B**

| Procedure | | Treatment and Follow-up Period | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2a** | **2b** | **3** | **4** | **5** | **6[a]** | **7[a]** | **8** | **9** | **EDV** |
| **Day** | **-7 to 1** | **1** | **8** | **15** | **29** | **91** | **181** | **189** | **210** | **271** | **361** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **+ 4** | **+ 3** | **± 10** | **± 14** | **NA** |
| Exploratory analysis serum sample | | X (predose) | | | X | X | X (predose) | | X | X | X | X |
| **Study intervention administration** | | X | | | | | X | | | | | |
| Injection site reaction monitoring | | X [j] | | | | | X [j] | | | | | |
| Immediate AEs [k] | | X | | | | | X | | | | | |

[a] Participants who do not receive an open-label dose of AZD5156 at Visit 5 will not be required to attend Visits 6 and 7.
[b] Perform predose and again 15 minutes (± 5 minutes) after both injections are complete.
[c] Sample urine test must return a negative result before dosing. Pregnancy testing prior to each dose must be on the same day as dosing and is especially important for female participants who had not reached menarche on enrollment into the study.
[d] Sites will be provided with rapid antigen tests.
[e] Baseline sample, not a screening sample; results not needed prior to dosing.
[f] To be performed for at least the first 600 participants in the Main Cohort.
[g] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[h] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[i] Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement.
[j] Perform immediately, 30 minutes (+ 10 minutes) after both injections are complete, and prior to participant release.
[k] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

Note: An early safety data review will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the Sentinel Safety Cohort, and enrollment of the Main Cohort will be initiated if the safety review concludes that the safety profile is acceptable.
ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; NA = not applicable; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

### 1.3.4 Follow-up Activities – Illness Visits for Participants with Qualifying Clinical Symptoms

**Table 4 Schedule of Activities for Illness Visits (Participants with Qualifying Clinical Symptoms)**

| **Procedure [a] and collection location** | **Site** | **Home** | **Home** | **Site [b]** | **Home** | **Site [b]** |
|---|---|---|---|---|---|---|
| **Day [c]** | **IL-D1** | **IL-D3** | **IL-D5** | **IL-D8** | **IL-D11** | **IL-D14** |
| **Window (days)** | **NA** | **± 1** | **± 1** | **± 1** | **± 1** | **± 2** |
| Medical history | X | | | X | | X |
| Targeted physical examination | X | | | X | | X |
| Vital signs (including pulse oximetry) | X | | | X | | X |
| Concomitant medication | X (ongoing observation and questioning) | | | | | |
| Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary) | X ← → | | | | | |
| Saliva sample for viral shedding [d] | X | X | X | X | X | X |
| SARS-CoV-2 RT-PCR (local laboratory) [e] | X | | | | | |
| NP swab SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel | X | | | X | | X |
| PBMCs for T-cell responses | X | | | X | | X |
| PK serum sample | X | | | X | | X |
| SARS-CoV-2 neutralizing antibody serum sample | X | | | X | | X |
| Exploratory analysis serum sample | X | | | X | | X |
| Telephone contact for safety monitoring | | X | | | | |

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the e-Diary.

[b] Where supported, home or mobile visits by study staff may substitute for site visits.
[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit day 1 = 1IL-D1, Illness Visit day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3 and so on as applicable.
[d] To be collected when operationally viable.
[e] A local test is required. If an immediate test result is not available, the participant should continue with the Illness Visit schedule until their result has been confirmed. Only if the local laboratory result is unavailable should the central laboratory result be used to assess continuation in Illness Visit schedule.

Note: The Illness Visit schedule is to be performed in addition to the Part A Main Cohort and Part B visit schedules. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

IL-D = illness day; NA = not applicable; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD5156, a combination of 2 mAbs, AZD1061 (cilgavimab, a component of AZD7442) and AZD3152, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19.

This Phase I/III study (D7000C00001) will assess the safety and neutralizing activity of AZD5156 in adults and adolescents 12 years of age or older (weighing at least 40 kg) with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. This study will bridge the established safety and efficacy of AZD7442 (AZD1061 and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan) to AZD5156 (AZD1061 and AZD3152) through the demonstration of comparable safety profiles and nAb titer responses to SARS-CoV-2 Alpha.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 22 September 2022, has caused over 610 million confirmed cases of COVID-19, including more than 6.5 million deaths, reported to the WHO (WHO 2022). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for the approximately 2% to 3% of the population who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. In the event that SARS-CoV-2 mutates into a strain for which currently available mAbs are ineffective, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein,

which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the RBD and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and nAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

Even with currently available mAbs, there is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 Combination Products - AZD5156 and AZD7442

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including AZD7442. The potency of AZD7442 was reduced with the emergence of the Omicron lineage, especially the Omicron variants BA.1 and BA.1.1 (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against the more recent Omicron variants BA.2, BA.3, and BA.4/5 (Tuekprakhon et al 2022). However, the loss of potency against BA.1 and BA.1.1 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD5156 is being developed to provide efficacy similar to that of AZD7442 but with greater breadth against variants not potently neutralized by AZD7442.

AZD5156 is comprised of a combination of 2 IgG1 mAbs: AZD1061 (cilgavimab, the component of AZD7442 with greater neutralization potency against the currently circulating Omicron variants) and AZD3152, a novel mAb chosen based on its improved breadth of coverage against Omicron variants compared to AZD7442, specifically high neutralizing potency against all the current Omicron variants. Thus, the combination of the 2 mAbs in AZD5156 has potent in vitro neutralization activity for all known current and past VOCs.

AZD1061 and AZD3152 bind to 2 distinct, non-competing epitopes on the SARS-CoV-2

spike protein receptor-binding domain. Like AZD1061, AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, which is expected to confer protection from COVID-19 for a duration of at least 6 months, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcRn or C1q binding, which is expected to reduce potential risk of ADE disease. Incorporation of these amino acid substitutions did not alter the neutralization potency of AZD7442 in vitro. Given both AZD5156 and AZD7442 target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD5156 builds upon the established safety and efficacy of AZD7442. AZD5156 is expected to have a similar safety and PK profiles and broader efficacy against a wider range of SARS-CoV-2 VOCs than AZD7442.

It is considered reasonable that AZD5156 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD5156 are similar to those of AZD7442.
- The nonclinical viral neutralization data against Omicron variants BA.1, BA.1.1, and BA.4/5 for AZD5156 are superior to those of AZD7442.
- AZD7442, which also includes AZD1061 (cilgavimab) as one of the 2 antibodies in the combination, has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD5156 include individuals who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications) or for whom vaccination is not suitable. Other situations where development of a broader protecting mAb such as AZD5156 may be of benefit include protection for health care workers and military personnel residing or working in high density settings, if a VOC that causes a higher mortality appears and can evade the protection acquired from currently available vaccines.

AZD5156 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 is provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

Like AZD7442, AZD5156 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither of the two mAbs which compose AZD5156 has any known human target. There are no identified risks for AZD5156 as no clinical data are currently available. However, there are clinical data for the AZD1061 (cilgavimab) mAb component in AZD5156, which formed half of the AZD7442 mAb combination product. Overall, the structural similarities between AZD5156 and AZD7442 suggest the anticipated safety profile of AZD5156 is expected to be similar to the observed safety profile of AZD7442; modifications made for AZD5156 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and ADE disease.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD5156 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD5156 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

For all mAbs, ADE disease is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of ADE disease involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. The disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry, is not expected with AZD5156 because, similar to AZD7442, the mAbs comprising AZD5156 have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of ADE occurring via this mechanism.

In the AZD7442 program, there was a small numerical imbalance for cardiac SAEs in the

pre-exposure prophylaxis study, PROVENT (D8850C00002). As of the 12-month data cut-off (April 2022), the number (proportion) of participants with an SAE under the MedDRA system organ class Cardiac disorders was 38 (1.1%) in the AZD7442 arm and 8 (0.5%) in the placebo arm. There was no clear temporal pattern and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no imbalances in cardiac SAEs have been observed in other AZD7442 clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for AZD7442 that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between AZD7442 and cardiac events has not been established.

### 2.3.2 Benefit Assessment

AZD5156 may be efficacious and offer participants protection from COVID-19. AZD5156 is similar to AZD7442 which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline has shown in the Phase III PROVENT trial (Levin et al 2022).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults and adolescents ≥ 12 years old who have a condition causing immune impairment, and thus may not mount an adequate immune response to COVID-19 vaccination, may benefit from AZD5156 for protection against COVID-19.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD5156 are justified by the anticipated benefits that may be afforded to participants who have conditions causing immune impairment and are at risk of severe COVID-19.

More detailed information about the known and expected benefits and potential risks of AZD5156 and AZD7442 is found in their respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Part A Objectives and Endpoints

**Table 5 Objectives and Endpoints – Part A**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD5156 and AZD7442 | Occurrence of AEs collected through Day 29<br>SAEs and AESIs collected throughout the study |
| To compare the nAb responses to the SARS-CoV-2 Alpha variant in serum following AZD5156 and AZD7442 administration | **Population**: SARS-CoV-2 nAb analysis set<br>**Endpoint**: GMTs for SARS-CoV-2 Alpha variant nAbs<br>**Intercurrent events**: Participants who experience a protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of the primary endpoint.<br>**Summary measure**: GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29). Descriptive statistics of SARS-CoV-2 nAb titers will be made by visit. |
| **Secondary** | |
| To compare the nAb responses to the SARS-CoV-2 Omicron variant BA.4/5 and the emerging dominant variant of concern circulating during the course of the study in serum following AZD5156 and AZD7442 administration | GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29).<br>Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, gSD, 95% CI, minimum, and maximum and summarized by treatment arm and visit |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death in participants receiving study intervention | Incidence of a post-treatment:<br>• Symptomatic COVID-19 case<br>• COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months)<br>• Severe COVID-19<br>• Composite of COVID-19 related hospitalization and/or COVID-19 related death (WHO COVID-19 Clinical Progression Scale score $\geq 4$)<br>• COVID-19 related hospitalization (separately)<br>• COVID-19 related death (separately) |

| Objectives | Estimand Description/Endpoints |
|---|---|
| To characterize the PK of AZD5156 and AZD7442 in serum | • In the Sentinel Safety Cohort: AZD5156, AZD1061, and AZD3152 concentrations over time and PK parameters (eg, $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{last}$, and $AUC_{inf}$)<br>• In the Main Cohort: AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To evaluate the ADA responses to AZD5156 and AZD7442 in serum | Incidence of ADA |
| **Exploratory** | |
| To assess the PK of AZD5156 and AZD7442 in nasal lining fluid | AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time |
| To characterize viral resistance to AZD5156 in participants with confirmed COVID-19 | Genotypic analysis and susceptibility analysis of SARS-CoV-2 variants to AZD5156 |
| To characterize the cellular immune responses to SARS-CoV-2 | Intracellular cytokine staining for SARS-CoV-2 T-cell responses at Illness Visits |
| To quantify SARS-CoV-2 viral load in participants with confirmed COVID-19 | Viral genome copies in NP swabs and saliva samples at Illness Visits as determined by RT-PCR |
| To assess additional immune responses in participants administered AZD7442 and AZD5156 | Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data |
| To characterize asymptomatic infection/seroresponse | The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; $AUC_{inf}$ = area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$ = area under the concentration-time curve at the last measured time point; CI = confidence interval; $C_{max}$ = maximum concentration; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; nAb = neutralizing antibody; NP = nasopharyngeal; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; $t_{max}$ = time to maximum serum concentration; WHO = World Health Organization

Note: Exploratory endpoints may be reported separately from the CSR.

## 3.2 Part B Objectives and Endpoints

### Table 6 Objectives and Endpoints – Part B

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To describe the safety of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Proportions of AEs through 29 days after second dose of study intervention given at 6 months<br>SAEs and AESIs through last visit (Visit 9) |
| **Secondary** | |
| To characterize the PK of an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 during Part A Main Cohort | Serum AZD5156, AZD1061, and AZD3152 concentrations |
| To characterize the PK of AZD1061, AZD3152, and AZD8895 during Part B among participants who received AZD7442 during Part A Main Cohort | Serum AZD1061, AZD3152, and AZD8895 concentrations |
| To describe ADA responses to an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Incidence of ADA following a dose of AZD5156 given at 6 months |
| To evaluate SARS-CoV-2 nAb levels in serum following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Post treatment GMTs and GMFRs from Visit 5 |
| **Exploratory** | |
| To describe the incidence of COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death during Part B | Incidence of post-treatment symptomatic COVID-19, severe COVID-19, COVID-19 related hospitalization, and COVID-19 related death |
| Explore additional biomarkers following an open-label dose of AZD5156 600 mg IM among participants who received AZD5156 or AZD7442 during Part A Main Cohort | Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data, including exploratory assays for biomarkers thought to play a role in COVID-19 severity or outcomes |

ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; nAb = neutralizing antibody; PK = pharmacokinetic(s); RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Note: Exploratory endpoints may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

D7000C00001 is a Phase I/III study that will be conducted in approximately 1256 participants to evaluate the safety and neutralizing activity of AZD5156.

The study will be conducted in 2 parts (Parts A and B). Part A consists of a Sentinel Safety Cohort and a Main Cohort.

The Part A Sentinel Safety Cohort will enroll 56 healthy adults, 18 to 55 years of age, who will be randomized (5:2) to receive AZD5156 (40 participants) or placebo (16 participants). Participants will be randomized to receive study intervention IM either in the gluteal or the anterolateral thigh, with the second component injection administered in the side contralateral to the first (gluteal or thigh, as applicable). Dosing within the Part A Sentinel Safety Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, and 2b). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Part A Main Cohort will be initiated if the safety review of all the Part A Sentinel Safety Cohort data (data up to Day 15) concludes that the safety profile is acceptable (for more details on the safety review, see Section 4.1.4). Part A Sentinel Safety Cohort randomization will be stratified by injection site (gluteal or anterolateral thigh). The duration of a Part A Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered.

Part A Main Cohort will enroll approximately 1200 participants, 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19. Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Dosing in the Part A Main Cohort will be staggered, so that no adolescent participants are dosed in the Part A Main Cohort until Day 15 safety data for at least 80 adult Part A Main Cohort participants (which will include at least 40 participants who have received AZD5156) have been reviewed by the DSMB to determine that there are no safety issues. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

After approximately 6 months from their Visit 1 dose, all active participants in the Part A Main Cohort of the study, regardless of whether they received AZD5156 or AZD7442, will continue to Part B of the study: an open-label administration of AZD5156. Consequently, Part B may include up to 1200 participants if all participants are eligible for Part B when

checked at Visit 5 (Day 181). For participants who take part in Part B, the follow-up will be 6 months from the open-label administration of AZD5156, and the total duration of involvement in the study for Part B participants will be approximately 12 months from the time of the first study intervention administration at Visit 1.

In total, in Part A of the study (Sentinel Safety and Main Cohorts), approximately 640 participants will be exposed to a single dose of AZD5156, 600 participants will be exposed to AZD7442, and 16 participants will be exposed to placebo. In Part B of the study, up to 1200 participants who participated in the Main Cohort of Part A will be exposed to a single dose of AZD5156; depending on their Part A randomization, this will be either their first or second dose of AZD5156.

The assigned study intervention (AZD5156 600 mg or AZD7442 600 mg) will be administered as 2 sequential IM injections in the thigh, one injection for each mAb component, with the second injection administered in the contralateral side. For AZD5156, AZD1061 (cilgavimab) should be administered first followed by AZD3152. For AZD7442 (EVUSHELD), AZD1061 (cilgavimab) should be administered first followed by AZD8895 (tixagevimab).

The study will be conducted at approximately 66 sites from approximately 15 countries.

Adverse events will be collected in the eCRF for 28 days after dosing: up to Visit 6 (Day 29) for Part A Sentinel Safety Cohort participants, Visit 3 (Day 29) for Part A Main Cohort participants, and from Visit 5 (Day 181) to Visit 7 (Day 210) for Part B participants. Serious adverse events and AESIs will be collected throughout the study. The duration of each participant's involvement in the study will be approximately 12 months from when the first study intervention is administered.

For the Main Cohort of Part A and Part B (open-label administration of AZD5156 at 6 months), following study intervention administration, if a participant believes he or she has contracted COVID-19, the Investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past 7 days and will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3). The Illness Visit schedule is to be performed in addition to the Main Cohort of Part A and Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Participants can receive SARS-CoV-2 vaccines after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

### 4.1.1 Part A Sentinel Safety Cohort

The first 56 participants in the study will comprise the Part A Sentinel Safety Cohort. Healthy adults 18 to 55 years of age who are enrolled in the Part A Sentinel Safety Cohort will be randomized to receive study intervention at 2 different IM administration sites, the gluteal and the anterolateral thigh. Participants in the Part A Sentinel Safety Cohort will be dosed as 4 subcohorts (Table 7). Dosing of the subcohorts will be sequential, with Subcohorts 1a/1b dosed first, followed by Subcohorts 2a/2b. Within each subcohort, participants will be randomized to receive AZD5156 or placebo in a 5:2 ratio.

**Table 7 Description of Part A Sentinel Safety Cohort**

| Subcohort | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| 1a | AZD5156 600 mg (5) | Placebo (2) | Gluteal |
| 1b | AZD5156 600 mg (5) | Placebo (2) | Anterolateral thigh |
| 2a | AZD5156 600 mg (15) | Placebo (6) | Gluteal |
| 2b | AZD5156 600 mg (15) | Placebo (6) | Anterolateral thigh |

IM = intramuscular; n = number of participants.

The ESDRs for the Part A Sentinel Safety Cohort will be conducted in 2 stages (as show in Figure 1):

- Enrollment will be paused once 14 participants have been recruited in the initial cohorts (1a and 1b). Initial ESDRs will be performed after the Visit 4 (Day 8) and Visit 5 (Day 15) safety data have been collected for Subcohorts 1a and 1b (a total of 14 participants). During the initial ESDRs, enrollment of participants will continue to be paused until after Day 15. If the ESDRs conclude that it is appropriate, then enrollment will be permitted to continue, and sites will be informed in writing that dosing of the Part A Sentinel Safety Cohort may continue with Subcohorts 2a and 2b. The pause and continuation of enrollment into each cohort will be managed via the IRT system to ensure no participants are enrolled until an ESDR decision to proceed has been met.
- Enrollment will be paused once more when 42 participants have been recruited into the final 2 cohorts (2a and 2b). Further ESDRs will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of the final 2 Part A Sentinel Safety Cohort Subcohorts 2a and 2b (a total of 42 participants).
- Enrollment of the Part A Main Cohort will only be initiated if the ESDR of all of the Part A Sentinel Safety Cohort (Subcohorts 1a, 1b, 2a, and 2b) to Day 15 demonstrates an acceptable safety profile.

The safety data collected will be entered into eCRFs and reviewed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The following safety parameters will be assessed as part of the ESDRs:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters (if available)

For more details on the ESDR, see Section 4.1.4.

### 4.1.2 Part A Main Cohort

The Part A Main Cohort of the study will enroll approximately 1200 participants 12 years of age or older with a minimum weight of 40 kg with conditions causing immune impairment, who are less likely to mount an adequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19 (Table 8). Dosing in the Part A Main Cohort will be staggered, so that it starts with adult participants aged 18 years and older, with no adolescent participants dosed in the Part A Main Cohort until safety data from Visit 2a (Day 8) and Visit 2b (Day 15) have been reviewed by the DSMB for at least 80 adult Part A Main Cohort participants (which will include approximately 40 participants who have received AZD5156).

Participants in the Part A Main Cohort will be randomized 1:1 to receive AZD5156 600 mg or AZD7442 600 mg administered IM in the anterolateral thigh. Participants must have conditions associated with immune impairment, and thus are most vulnerable to developing severe COVID-19 due to their expected inability to respond adequately to SARS-CoV-2 vaccines, to be eligible for this study. Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2 infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No).

**Table 8 Description of Part A Main Cohort**

| Population | Active Treatment (n) | Control Treatment (n) | IM administration site |
|---|---|---|---|
| Adults and adolescents ≥ 12 years of age with conditions associated with immune impairment | AZD5156 600 mg (600) | AZD7442 600 mg (600) | Anterolateral thigh |

IM = intramuscular; n = number of participants

Part A Main Cohort participants are planned to be monitored for approximately 12 months from Visit 1 for safety, PK, and ADA assessments.

Planned analyses are discussed in Section 9.5.

### 4.1.3 Part B

Part A Main Cohort participants will become eligible for joining Part B of the study once they reach Day 181 (+ 4 days) in the Part A Main Cohort (see Section 1.3.3). The dosing interval between Dose 1 (Part A Main Cohort, Day 1) and Dose 2 (Part B, Day 181) will be approximately 6 months. Participants will not need to be reconsented to take part in Part B of the study and will keep the same ID number from Part A. Part B participants will NOT be unblinded from their Part A treatment arm. All participants will receive AZD5156 600 mg IM regardless of original treatment arm in Part A. As with the Part A Main Cohort, AZD5156 will be administered IM in the anterolateral thigh in Part B. Part B participants will be followed for 6 months post the Part B dose, for a total duration in the study of 12 months from Visit 1 of the Part A Main Cohort. Part B participants who develop COVID-19 qualifying symptoms after Visit 5 (Day 181) will be instructed to initiate Illness Visits.

Participants from the Part A Sentinel Safety Cohort will not be eligible for Part B.

### 4.1.4 Safety Review

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs of Part A Sentinel Safety Cohort data, as discussed in Section 4.1.1.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the Part A and Part B Main Cohort of the study, as discussed in Section 9.7.

## 4.2 Scientific Rationale for Study Design

The overall study design is similar to the previous AZD7442 Phase I study in pre-exposure prophylaxis (D8850C00001) and the AZD7442 Phase III efficacy study (D8850C00002/PROVENT) as well as other study designs evaluating SARS-CoV-2 mAbs (Levin et al 2022, Fact Sheet EUA Bebtelovimab 2022, Gupta et al 2021, Weinreich et al 2021). The primary endpoints are standard safety assessments and the GMTs of SARS-CoV-2 Alpha variant nAbs.

### 4.2.1 Rationale for Administration Site

The clinical studies which supported the EUA in the US, and the marketing authorization application in the EU, administered AZD7442 by IM in the gluteal region; however, healthcare providers have provided feedback on the challenges of administering AZD7442 in the gluteal region in a mass clinic setting and in obese individuals. Thus, off-label use of AZD7442 administered IM in the deltoid or anterolateral thigh has been reported. Since the anterolateral thigh region is a preferred IM administration site by healthcare providers compared to the gluteal area, participants in the Part A Sentinel Safety Cohort of the study will receive study intervention in either the gluteal or anterolateral thigh to compare safety and PK data for both sites of administration. Part A Main Cohort and Part B participants will all

receive study intervention in the anterolateral thigh to decrease variability in the PK and nAb analyses. The assigned study intervention will be administered as 2 sequential IM injections, one injection for each component, with the second injection administered in the contralateral side (gluteal or thigh, as applicable) to limit the injection volume into the muscle to reduce the risk of local site reactions.

### 4.2.2 Rationale for Study Population

The Part A Sentinel Safety Cohort will be conducted in adults 18 to 55 years of age, as was done for the AZD7442 Phase I study (D8850C00001). Initial evaluation of AZD5156 in this cohort allows for safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

The Part A Main Cohort will be conducted in adolescents and adults 12 years of age or older with conditions causing immune impairment (ie, the current main target population using AZD7442) as these individuals are not expected to mount an adequate immune response to SARS-CoV-2 vaccination and thus remain at high risk of severe COVID-19. The inclusion criteria for the Part A Main Cohort are designed to select for these individuals (for list of conditions, see Section 5.2.1). Part A Main Cohort participants will also take part in Part B.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD5156 Dose

The dose level of AZD5156 600 mg for administration in this study was chosen based on all available nonclinical animal models, nonclinical pharmacology, and PK data for AZD5156 as well as the nonclinical and clinical PK data and clinical safety data for AZD7442. Similar PK for AZD5156 and AZD7442 have been observed in human FcRn transgenic mice and are expected to be observed in non-human primates. Based upon population PK modeling, assuming the same PK and partitioning into the nasal lining fluid as AZD7442, 600 mg of AZD5156 is predicted to maintain nasal lining fluid concentrations of AZD5156 above the $IC_{90}$ for the BA.1, BA.1.1, BA.2, and BA.4/5 variants of SARS-CoV-2 in at least 70% of study participants for greater than 6 months.

### 4.3.2 Justification for AZD7442 Dose

Available PK modeling data demonstrate that, at a dose of 600 mg IM, the median AZD7442 serum concentrations exceed the modelled concentration needed to prevent disease caused by BA.2/3/4/5 subvariants for 6 months. These data, together with in vitro neutralization data for emerging VOCs, favorable efficacy and safety results from the AZD7442 Phase III (PROVENT/D8850C00002/NCT04625725 and TACKLE/D8851C00001/NCT04723394) studies, and real-world evidence studies assessing AZD7442 (Al Jurdi et al 2022), validate the AZD7442 prophylactic dose of 600 mg IM in this study.

### 4.3.3 Justification for Placebo

Placebo will be administered in a small population (16 participants) of healthy individuals at low risk of development of severe COVID-19 in order to provide a blinded comparison in the Sentinel Safety Cohort and to allow objective assessment of the safety of AZD5156. A similar placebo-controlled study design in healthy adults was used in the AZD7442 Phase I study (D8850C00001).

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the appropriate SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the appropriate SoA (Section 1.3) for the last participant in the study globally.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 For Part A Sentinel Safety Cohort Participants (Phase I)

### 5.1.1 Inclusion Criteria

Participants are eligible to be included in the Part A Sentinel Safety Cohort only if all of the following criteria apply:

1 Healthy participants according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator, with no concomitant disease or concomitant medication (except for medication specifically permitted by the protocol).
2 Age 18 to 55 years at the time of signing the informed consent.
3 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
4 Able to attend all scheduled visits and to comply with all study procedures.
5 Negative rapid antigen test at Visit 1.
6 Weight ≥ 45 kg and ≤ 110 kg at screening.
7 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.1.2 Exclusion Criteria

Participants are excluded from the Part A Sentinel Safety Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration.
   – Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
      o Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.

- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

– Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

– The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

– All female participants of childbearing potential must have a negative urine pregnancy test result at screening.

– Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the screening period or may be rescreened once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Receipt of immunoglobulin (non-COVID related) or blood products within 6 months prior to Visit 1.

8 Previous receipt of a mAb against SARS-CoV-2.

9 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

10 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

11 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

12 Known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening.

13 Active infection with hepatitis B or C.

14 Serum creatinine, AST, or ALT above the ULN or hemoglobin, white blood cell count, or platelet count below the lower limit of normal at screening.

15 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

16 Any laboratory value in the screening panel that, in the opinion of the Investigator, is clinically significant or might confound analysis of study results.

17 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

18 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

19 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

20 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.2 For Part A Main Cohort Participants (Phase III)

### 5.2.1 Inclusion Criteria

Participants are eligible to be included in the Part A Main Cohort only if all of the following criteria apply:

1 Participant must be 12 years of age or older at the time of signing the informed consent.

2 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations. For participants from 12 to < 18 years of age, their

parents or legal guardians must give their signed written informed consent, as appropriate, and participants will sign an assent form.

3 Able to attend all scheduled visits and to comply with all study procedures.

4 Negative rapid antigen test at Visit 1.

5 Weight ≥ 40 kg at Visit 1.

6 Participants must satisfy at least 1 of the following risk factors at enrollment:

- Have cancer (eg, active solid tumors and hematologic malignancies) except for adequately treated:
  - Non-melanoma skin cancer or lentigo maligna
  - Uterine cervical carcinoma in situ
  - Local prostate carcinoma
- Have solid organ transplant or a hematopoietic stem cell transplant (within 2 years of transplantation, are taking immunosuppression therapy or who have chronic graft-versus-host disease)
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], high-dose alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy
- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, agammaglobulinemia)

7 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

8 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the Investigator.

### 5.2.2 Exclusion Criteria

Participants are excluded from the Part A Main Cohort if any of the following criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.
- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion,

intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

7 Has HIV infection.

8 Receipt of convalescent COVID-19 plasma treatment within 6 months prior to Visit 1.

9 Previous receipt of a mAb against SARS-CoV-2 within 6 months prior to Visit 1.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 COVID-19 within 6 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at-home testing]).

12 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

13 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

14 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

15 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

16 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 For Part B Participants

### 5.3.1 Inclusion Criteria

Participants from the Part A Main Cohort are eligible to be included in Part B only if all of the following criteria apply:

1 Participant has been randomized into the Part A Main Cohort and is 181 days or more post first dose (Visit 1).

2 The participant must still satisfy at least 1 of the risk factors that were required for inclusion in the Part A Main Cohort (inclusion criterion 6 for the Part A Main Cohort; Section 5.2.1).

3 Weight ≥ 40 kg at Visit 5.

4 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease.

5 Documented negative rapid SARS-CoV-2 antigen test at Visit 5 (Day 181) prior to dosing.

6 WOCBP must not be pregnant or lactating, and must still be using a highly effective method of contraception or abstinence until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

### 5.3.2 Exclusion Criteria

Participants are excluded from Part B if any of the following exclusion criteria apply:

1 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study intervention administration and until at least 6 months after study intervention administration. Note: female participants aged > 12 years will be considered to be a woman of childbearing potential.

- Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:
  - Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly.

Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

- The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- Highly effective birth control methods include: Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

2 Known hypersensitivity to any component of the study intervention.

3 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

4 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

5 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

6 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

7 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

8 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

9 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

10 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD5156 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.4 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Sections 5.1.2 and 5.2.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility. Only a single rescreening is allowed in the study and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio), and in the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). All participants in Part B will receive AZD5156. Details of these study interventions are presented in Table 9.

AZD5156 consists of AZD1061 and AZD3152 contained in separate vials. AZD7442 consists of AZD1061 and AZD8895 contained in separate vials. Each vial of AZD1061, AZD3152, or AZD8895 contains colorless to slightly yellow, clear to opalescent solutions for injection. For AZD5156 in the Part A Sentinel Safety Cohort, label-claim volume per vial is 1.5 mL for AZD1061 and 2 mL for AZD3152; for AZD5156 in the Part A Main Cohort and Part B, label-claim volume per vial is 2 mL for each component; and for AZD7442, label-claim volume per vial is 1.5 mL for each component.

AZD5156 or AZD7442 will each be administered as 2 IM injections, one injection for each component mAb, with the second injection administered in the contralateral side (gluteal or thigh, as applicable). If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

For AZD5156, AZD1061 should be administered first followed by AZD3152. For AZD7442, AZD1061 should be administered first followed by AZD8895.

The AZD3152 component of AZD5156 will be derived from 2 sources: cell pools material and clonal cell material from a single production cell line which will form a Master Cell Bank and constitute the source of the commercial supply. In the Part A Sentinel Safety Cohort, participants will receive only cell pools material. In the Part A Main Cohort, participants will receive only clonal cell material.

The AZD1061 component of AZD5156 will initially be supplied from the AZD7442 clonal cell material for the Part A Sentinel Safety Cohort. A more concentrated formulation for AZD1061 will be administered to participants in the Part A Main Cohort and in Part B.

**Table 9 Investigational Medicinal Products – Part A**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Type** | Drug | Drug | Drug | Placebo |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each AZD1061 vial contains 150 mg solution for injection. The solution contains 100 mg/mL of AZD1061 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.<br>Each AZD3152 vial contains 300 mg solution for injection. The solution contains 150 mg/mL of AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | AZD7442 will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. | 0.9% sodium chloride for injection |

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152) for Sentinel Safety Cohort** | **AZD5156 (AZD1061 + AZD3152) for Main Cohort** | **AZD7442 (AZD1061 + AZD8895)** | **Placebo** |
|---|---|---|---|---|
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 at 100 mg/mL and 300 mg AZD3152 at 150 mg/mL | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL | 600 mg AZD7442 consisting of 300 mg AZD1061 and 300 mg AZD8895, both at 100 mg/mL | 0.9% sodium chloride for injection |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) | 600 mg single dose of AZD7442<br>(300 mg of AZD1061 and 300 mg of AZD8895) | Single dose |
| **Route of administration** [a] | 2 IM injections; 3 mL of AZD1061<br>2 mL of AZD3152 | 2 IM injections of 2 mL each | 2 IM injections of 3 mL each | 2 IM injections of 2 mL each |
| **Use** | Investigational | Investigational | Active-comparator | Placebo-comparator |
| **IMP and NIMP** | IMP | IMP | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca | AstraZeneca | Study site |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | Dependent on study site |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

[a] The second injection will be administered in the contralateral side.

**Table 10 Investigational Medicinal Products – Part B**

| **Intervention name** | **AZD5156 (AZD1061 + AZD3152)** |
|---|---|
| **Type** | Drug |
| **Dose formulation** | AZD5156 will be supplied as separate vials of AZD1061 and AZD3152.<br>Each vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD1061 or AZD3152 in 20 mM L-histidine/L-histidine hydrochloride, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. |
| **Unit dose strength(s)** | 600 mg AZD5156 consisting of 300 mg AZD1061 and 300 mg AZD3152, both at 150 mg/mL |
| **Dosage level(s)** | 600 mg single dose of AZD5156<br>(300 mg of AZD1061 and 300 mg of AZD3152) |
| **Route of administration** | 2 IM injections of 2 mL each |
| **Use** | Investigational |
| **IMP and NIMP** | IMP |
| **Sourcing** | AstraZeneca |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. |

IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; w/v = weight per volume.

## 6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

In the Part A Sentinel Safety Cohort, participants will be randomized to receive AZD5156 or placebo (5:2 ratio) stratified by injection site (gluteal or anterolateral thigh). In the Part A Main Cohort, participants will be randomized to receive AZD5156 or AZD7442 (1:1 ratio). Part A Main Cohort randomization will be stratified by SARS-CoV-2 vaccination status within 6 months prior to randomization (Yes, No), prior SARS-CoV-2-infection within 6 months prior to randomization (Yes, No), and AZD7442 (EVUSHELD) use within 12 months prior to randomization (Yes, No). Part B has an open-label design (all participants will receive AZD5156) and so there will be no randomization required for that cohort.

All participants in the Part A Sentinel Safety Cohort and Part A Main Cohort will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoAs (Section 1.3).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

For the Part A Sentinel Safety Cohort and Part A Main Cohort, neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD5156, AZD7442, and placebo are visually distinct prior to dose preparation (due to differences in vial volumes and container closure), study intervention will be handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations. Syringe masking will be required in order to maintain the blind. The Investigator responsible for safety assessment will not attend the study intervention administration session but will be available in case of emergency (eg, anaphylactic shock).

The following personnel will have access to the randomization list during the study, prior to DBL:

- Those carrying out the packaging and labeling of IMP
- Those generating the randomization list
- The AstraZeneca supply chain department
- The unblinded AstraZeneca monitor or designee (if applicable)

- Bioanalytical PK and ADA laboratories responsible for analyzing the samples.
- The DSMB.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Participants who participate in Part B of the study will not be unblinded for what study intervention they received at Part A Main Cohort Visit 1.

### 6.3.3 Procedures for Unblinding

The IRT/RTSM will be programmed with blind-breaking instructions. Unblinding should only occur within the IRT/RTSM system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives

during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Table 11 lists the permitted and restricted, medications during the study.

**Table 11 Permitted, Restricted, and Prohibited Medications**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | Licensed influenza vaccines are permitted at any time.<br>All other vaccines except SARS-CoV-2 vaccines (see below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening (Part A Sentinel Safety Cohort) or Visit 1 (Part A Main Cohort) and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

## 6.6 Dose Modification

Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Each participant in Part A will receive a single dose of study intervention (divided into 2 separate doses for each mAb component for AZD5156 or AZD7442). Participants in Part B will receive a second dose of study intervention (open-label AZD5156 for all Part B participants) approximately 6 months after the first dose. For each dosing occasion, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance,

or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Section 1.3).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

### 7.2.1 Stopping Rules for Part A Sentinel Safety Cohort

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD5156:

- An SAE considered at least possibly related to the study intervention by the Investigator or AstraZeneca in any one participant.
- Grade 3 or higher anaphylactic reaction (per NIAID and the FAAN definition; see Appendix E) considered related to the study intervention by the Investigator or AstraZeneca in any participant.
- Any safety finding assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until fully assessed.

In the event of a temporary hold for any of the above criteria, the risk to all participants will be evaluated thoroughly by AstraZeneca prior to a decision as to whether to terminate the study prematurely or continue dosing.

### 7.2.2 Stopping Rules for Part A Main Cohort and Part B

The study will be put on temporary hold (defined as a pause in enrollment of participants into the Part A Main Cohort and/or dosing of participants in Part B) pending further safety data

analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca, warrants suspension of further dosing of participants until the safety finding is fully assessed.

In the event of a temporary hold for safety reasons, AstraZeneca will carefully review the totality of data, and the risk to all participants will be evaluated by AstraZeneca thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing.

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon

occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy Assessments

### 8.1.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for Part A Main Cohort/Part B). Authorized laboratories will measure nAbs to the SARS-CoV-2 Alpha variant, the Omicron variant BA.4/5, and the emerging dominant variant circulating during the course of the study, using validated pseudovirus neutralization assays for the specified variants.

### 8.1.2 Participant-reported COVID-19 Symptoms

To determine the incidence of infection, study sites will contact all participants weekly (telephone/email/text) with reminders to monitor for COVID-19 symptoms.

During these contacts, the Investigator will assess whether the participants meet the clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020) from the past week/month. For participants in the Part A Main Cohort and Part B, the Investigator site will need to conduct Illness Visits within 3 days if such symptoms are reported (see Section 8.1.3 for more on Illness Visits). Participants who present with clinical criteria for SARS-CoV-2 infection, must contact the study site.

Clinical criteria for SARS-CoV-2 infection (as defined by WHO 2020):

- Acute onset of fever and cough together
  OR
- Acute onset of any 3 or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza (runny nose), dyspnea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Participants who present with a COVID-19 qualifying symptom(s) after Visit 1 in the Part A Main Cohort or after Visit 5 (Day 181) for participants in Part B will be instructed to initiate Illness Visits as described in Section 8.1.3. Qualifying COVID-19 symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia ($SpO_2$ < 90% in room air and/or severe respiratory distress), and a WHO Clinical Progression Scale score of 5 or higher (Table 12).

**Table 12 WHO Clinical Progression Scale**

| Patient State | Descriptor | Score |
|---|---|---|
| Uninfected | Uninfected, no viral RNA detected | 0 |
| Ambulatory mild disease | Asymptomatic; viral RNA detected | 1 |
| | Symptomatic; independent | 2 |
| | Symptomatic; assistance needed | 3 |
| Hospitalized: moderate disease | Hospitalized; no oxygen therapy [a] | 4 |
| | Hospitalized; oxygen by mask or nasal prongs | 5 |
| Hospitalized: severe disease | Hospitalized; oxygen by NIV or high flow | 6 |
| | Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ | 7 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors | 8 |
| | Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO | 9 |
| Dead | Death | 10 |

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO = extracorporeal membrane oxygenation; $FiO_2$ = fraction of inspired oxygen; NIV = non-invasive ventilation; $pO_2$ = partial pressure of oxygen; $SpO_2$ = oxygen saturation.
Source: WHO Working Group 2020

### 8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.2) in the Part A Main Cohort or Part B

will be tested locally for SARS-CoV-2 and will be instructed to visit the study site for initiation of illness assessments (Table 4); where supported, home or mobile visits may be substituted for the site visits. Part A Sentinel Safety Cohort participants will not take part in the Illness Visits.

Symptomatic participants will complete IL-D1 and will be instructed to continue with the home collection requirements. Symptomatic participants will continue with the Illness Visits until a laboratory result is available. Only participants who test positive by the local laboratory results will be instructed to continue with the Illness Visits, including home collection requirements. All home laboratory kits should be brought to all subsequent Illness Visits. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and home laboratory kits. Participants will continue with the main scheduled assessments (ie, Table 2 or Table 3).

Throughout the Illness Visit, the participants should record symptoms associated with COVID-19 in an Illness e-Diary daily.

The Illness Visit schedule is to be performed in addition to the Part A Main Cohort/Part B visit schedule. If these visits overlap according to respective visit windows, a single visit may be done with the combined study procedures completed once.

The Illness Visit assessment pathway may be initiated more than once for each participant, if considered necessary.

#### 8.1.3.1 SARS-CoV-2 Testing and Other Virology Assessments

At IL-D1, nasopharyngeal swabs will be collected and tested for SARS-CoV-2 by authorized RT-PCR assays at local and central laboratories (Section 8.2.3).

Resistance monitoring as performed by genotypic sequencing analysis and phenotypic characterization of virus identified from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Section 1.3).

### 8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoAs (Section 1.3).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following randomization should be reported as an AE per Section 8.3.

All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

### 8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoAs (Section 1.3). The vital signs assessments at the Illness Visits (see Section 8.1.3) will also include pulse oximetry.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.6.

### 8.2.3 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for the Part A Sentinel Safety Cohort only (see Section 1.3.1 and Section 1.3.2). Clinical safety laboratory assessments will not routinely be performed for the Part A Main Cohort or during Part B.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 13.

**Table 13 Laboratory Safety Variables**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | |
| Glucose | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) |

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.
ULN = upper limit of normal

For female participants aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine pregnancy test will be performed using a local laboratory at screening (Part A Sentinel Safety Cohort), Visit 1 (Part A Main Cohort), or at Visit 5 (Part B). Where the tests are performed on a dosing day, the test must be performed on the same day as the dose is administered, prior to dosing. The test must be negative before dosing. This is especially important for any female participants who have not reached menarche at enrollment into the study and whose child bearing potential is expected to change during the study.

## 8.2.4 Other Safety Assessments

### 8.2.4.1 Immediate Adverse Events

Participants will be kept under observation for 1 hour after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source

document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Any AEs should be reported as described in Section 8.3.

#### 8.2.4.2 Injection Site Reactions

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection.

Injection site reactions will be monitored on study days where study intervention is administered. The injection site monitoring will be performed immediately after and 30 minutes (+ 10 minutes) after both injections are complete and also prior to participant release.

Any AEs should be reported as described in Section 8.3.

## 8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 29 days following administration of study intervention. Any AESIs will be programmatically identified and assessed from the time of study intervention (see Section 8.3.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or

her, the Investigator shall, without undue delay, report the serious adverse event to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be collected according to the time points specified in the SoAs (Section 1.3).

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious. The AESIs will be programmatically identified through AE information that is collected in the eCRF.

The AESIs for AZD5156 and AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Cardiovascular and thrombotic events

### 8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs.

Where AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.8 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for both AZD5156 and the active comparator product AZD7442 are the respective Investigator's Brochures for the individual products.

### 8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

#### 8.3.9.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the

participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.10 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.8) and **within 30 days** for all other medication errors.

#### 8.3.10.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.3.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

## 8.4 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is

specified in this protocol will be considered an overdose (see Table 9).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

Characterization of the PK of AZD5156 and AZD7442 in serum is a secondary objective of

this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoAs (Section 1.3).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum concentrations of AZD5156 and each component mAb (AZD1061 and AZD3152) from the Part A Sentinel Safety Cohort will be used to estimate PK parameters for each mAb and the combination of two mAbs (see Section 8.5.1.2). Serum concentrations of AZD5156 and AZD7442 from the Part A Main Cohort and nasal fluid concentrations over time from both cohorts will be evaluated. Serum concentrations of AZD5156 and AZD7442 (and/or component mAbs) will also be evaluated for Part B.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentrations of AZD5156 and AZD7442, in total and for each component mAb, in serum and nasal fluid will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. Serum samples at time points matching nasal fluid sample collection can also be used to assess urea concentration for normalization of the nasal fluid PK measurement. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

#### 8.5.1.2 Pharmacokinetic Parameters

In the Part A Sentinel Safety Cohort, the following PK parameters will be estimated (where possible) from serum concentrations of AZD5156, AZD1061, and AZD3152:

- $C_{max}$;
- $t_{max}$;
- $t_{½}$;
- $AUC_{last}$

- $AUC_{inf}$.

### 8.5.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoAs (Table 2 for the Part A Sentinel Safety Cohort and Table 3 for the Part A Main Cohort/Part B). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.2.1 Antidrug Antibody Assessments

Blood samples for determination of ADA to AZD5156 and AZD7442 in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and anti-drug nAbs analysis (anti-drug nAbs – Part A Main Cohort and Part B only).

#### 8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 nucleocapsid protein antigen assay operated by an authorized laboratory.

#### 8.5.2.3 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral, mucosal, and/or cellular immune responses, as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

### 8.5.3 Pharmacodynamics

Pharmacodynamics will not be evaluated.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

#### 8.6.1.1 Virologic Assessments

Nasopharyngeal swabs from Illness Visits will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoAs (Section 1.3). Instructions for obtaining and processing nasopharyngeal swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by a recombinant SARS-CoV-2 spike-pseudovirus neutralization assay.

Local and central assessments should be collected per the SoAs (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

### 8.6.2 Other Study-Related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, peripheral blood mononuclear cells, or mucosal specimens to evaluate their association with observed clinical responses to AZD5156.

For storage, re-use and destruction of biomarker samples see Section 8.5.

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Data from the Part A Sentinel Safety Cohort will be presented separately from the Part A Main Cohort and Part B. Participants' data will be presented by the dosing regimen received. Analysis of Part B endpoints will be descriptive only; there will be no direct comparisons with Part A data.

## 9.1 Statistical Hypotheses

The primary objectives for Part A are to evaluate the safety of AZD5156 and AZD7442 and to compare the serum GMTs of nAbs for the SARS-CoV-2 Alpha variant in participants receiving AZD5156 or AZD7442. The primary objective for Part B is to describe the safety of a dose of AZD5156 among participants who received AZD5156 or AZD7442 6 months prior.

In the Part A Main Cohort, a noninferiority comparison will be performed using the ratio of GMTs at Visit 3 (Day 29) of Alpha variant nAbs for participants receiving AZD5156 versus AZD7442 with a noninferiority threshold of 2/3. This threshold implies with 95% confidence that the serum GMTs of Alpha variant nAbs in participants receiving AZD5156 will retain at least 2/3 of the neutralizing activity compared to participants receiving AZD7442 at Visit 3 (Day 29).

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the GMTs of Alpha variant nAbs in participants receiving AZD5156 are not inferior to those in participants receiving AZD7442 within the noninferiority margin.

Null hypothesis: GMT ratio $\leq 2/3$

Alternative hypothesis: GMT ratio $> 2/3$

## 9.2 Sample Size Determination

Approximately 1256 adults will be randomized in the study. In the Part A Sentinel Safety Cohort, 56 healthy adults 18 to 55 years of age will be randomized to receive either AZD5156 (40 participants in total) or placebo (16 participants in total). In the Part A Main Cohort,

approximately 1200 additional participants 12 years of age or older will be randomized 1:1 to receive AZD5156 or AZD7442. All 1200 participants in the Part A Main Cohort will be considered for inclusion in Part B.

The sample size of 1200 participants in the Part A Main Cohort was chosen to support immunobridging to AZD7442 through assessment of the primary objective of noninferiority of Alpha variant SARS-CoV-2 nAb serum GMTs at Visit 3 (Day 29) in participants administered AZD5156 compared to those administered AZD7442. Assumptions are based on data from prior studies with AZD7442. The assumed gSD was modeled from the PROVENT study and adjusted to account for differences in the target populations. The sample size is sufficient to provide > 90% power to declare noninferiority using a lower threshold of 2/3 assuming a true GMT ratio of 1.0 and 85% power with a GMT ratio of 0.9. These calculations assume a gSD of 5.0, a 1-sided Type I error rate of 2.5%, and a 10% attrition rate.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 14 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. |
| SARS-CoV-2 neutralizing antibody analysis set | All participants in the FAS with baseline and postdose antibody measurements with quantifiable SARS-CoV-2 serum titers. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |
| Antidrug antibody analysis set | All participants in the FAS with baseline and postdose antidrug antibody result. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. |

mAb = monoclonal antibody; PK = pharmacokinetics; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 9.4 Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints in the Part A Main Cohort and descriptive objectives for Part B.

### 9.4.1 General Considerations

Part A of this study is designed to evaluate AZD5156 compared to AZD7442 for noninferiority of the nAb GMTs for the SARS-CoV-2 Alpha variant. To align with the PK and nAb analysis sets, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Categorical variables will be summarized using frequency and percentages, where the

denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

The analyses of the primary endpoints are described in Section 9.4.3 (SARS-CoV-2 nAb responses) and Section 9.4.5 (safety).

#### 9.4.2.2 Secondary Endpoint(s)

The analysis of the Part A secondary endpoints of SARS-CoV-2 nAb responses against Omicron variant BA.4/5 and the emerging dominant variant circulating during the course of the study is described in Section 9.4.3.

The analysis of the secondary endpoint of AZD5156 and AZD7442 PK is described in Section 9.4.6.

Other secondary endpoints include the summary measures listed below. Each COVID-19 efficacy endpoint is derived as a binary outcome where each participant is to have a negative SARS-CoV-2 RT-PCR test at baseline. Each outcome will be evaluated through Day 181 (Part A Main Cohort) and Day 361 (Part A Sentinel Safety Cohort and Part B) where a participant can become positive at any time between the baseline and evaluation point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. COVID-19 efficacy will be presented as descriptive counts and percentages by treatment arms. If sufficient events accumulate a formal comparison of efficacy will be conducted as prespecified in the SAP.

- Incidence of post treatment symptomatic COVID-19 infection
- Incidence of post treatment COVID-19 infection
- Incidence of severe COVID-19
- Incidence of the composite of COVID-19 related hospitalization or COVID-19 related death
- Incidence of COVID-19 related hospitalization
- Incidence of COVID-19 related death
- Asymptomatic infections determined by serology assays

#### 9.4.2.3 Exploratory Endpoint(s)

Details of the analyses for the exploratory endpoints will be specified in a separate Exploratory SAP and reported separately from the primary analysis.

### 9.4.3 SARS-CoV-2 Neutralizing Antibody Responses

All immunogenicity endpoints will be summarized descriptively by strain, treatment arm, and time point. Participants with a positive SARS-CoV-2 RT-PCR test at baseline will be excluded from the analysis. Comparisons of SARS-CoV-2 nAb titers between treatment groups will be conducted using GMT ratio. The primary analysis will be evaluated with an ANCOVA model which will include fixed effects for baseline nAb concentrations, age categories, prior vaccination, and prior COVID-19 infection. Additional sensitivity analysis will explore other relevant prognostic factors. Details will be specified in the SAP on each analysis.

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in Alpha variant nAb levels. The secondary endpoints of SARS-CoV-2 nAb responses against the Omicron BA.4/5 variant and the emerging dominant variant circulating during the course of the study will also be evaluated in Part A. The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.4 Antidrug Antibody Variables

Antidrug antibody variables include status (positive or negative) and titer as follows:

- Total number of participants with negative ADA assay response at all times
- Total number of participants with positive ADA assay response at any time
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay
- Titer values
- Titer category

The ADA variables will be assessed and summarized by number and percentage of

participants by treatment group. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs), PK, and efficacy will be assessed.

### 9.4.5 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA (at the time of reporting), and will be summarized by system organ class and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.6 Pharmacokinetics

Following a single dose of AZD5156 or AZD7442, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group in the Part A Main Cohort over time.

Noncompartmental PK data analysis will be performed for AZD5156-treated participants in the Part A Sentinel Safety Cohort after the 3-month primary data readout (see Section 9.5). Pharmacokinetic parameters will be estimated for each individual mAb and the combination of the 2 component mAbs of AZD5156. The following single-dose serum PK parameters will be estimated: $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, $t_{½}$.

A population PK analysis will be performed for the combined Part A and Part B data and will be reported separately.

## 9.5 Planned Analyses

No interim analyses are planned. The primary analyses will occur after all Part A Main Cohort participants have completed Visit 4 (Day 91) or have withdrawn from the study. In addition, a final analysis will occur once all participants have completed their end of study visit. A total of 2 prespecified analyses are intended. The study will maintain a double-blind period until the primary analysis (ie, blind for participants, Investigators/site staff, and AstraZeneca/designated clinical research organization). To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the Part A treatment assignment until the end of the study and final readout. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in an Study Integrity Plan. Participant-level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented. The final analysis will include data from both study periods, Part A and Part B (open-label administration of AZD5156 at 6 months). The SAP will describe the 2 planned analyses in greater detail.

Should an emerging VOC significantly affect the neutralization activity of AZD7442, and there is a medical need for AZD5156 to be submitted for health authority review urgently, additional analysis will be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Safety Review Committee

An internal Safety Review Committee will be assembled by the Sponsor to perform the ESDRs for the Part A Sentinel Safety Cohort , as discussed in Section 4.1.1.

## 9.7 Data Safety Monitoring Board – Part A and Part B Main Cohort

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data from the Part A and Part B Main Cohort in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and DBL.

The DSMB will also perform an unblinded review of the Day 15 safety data of at least the first 80 adult participants (including at least 40 adult participants who have received AZD5156) to determine that there are no safety issues and to allow the start of enrollment of adolescents into the Part A Main Cohort.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a

DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# Appendix A Regulatory, Ethical, and Study Oversight Considerations

## A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Pediatric participants (ie, those aged 12 to < 18 years for the Part A Main Cohort) will be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be

destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant

and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a

'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## B 4 Medication Error, Drug Abuse, and Drug Misuse

**Medication Error**

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

**Drug Misuse**

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

## C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
  - Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

## Hy's Law Laboratory Kit for Central Laboratories

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal

# Appendix E Anaphylaxis

The NIAID and FAAN clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

(a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

(a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure

(b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table 15, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

**Table 15 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

| | | |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately |

| | | |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care

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| **Clinical Study Protocol Addendum** | |
|---|---|
| Study Intervention | AZD3152 |
| Study Code | D7000C00001 |
| Version | 2.0 |
| Date | 13 June 2023 |

# A Phase II Open Label Sub-study to Evaluate the Safety, PK, and Neutralizing Activity of AZD3152 for Pre-exposure Prophylaxis of COVID-19

## Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA) Sub-study

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: 151, 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s): IND Number 161539**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D7000C00001**

**Version Number:** 2.0

- **Study Intervention:** AZD3152 monoclonal antibody and AZD7442 (EVUSHELD™), the active comparator

**Study Phase:** II

**Title:** A Phase II Open Label Sub-study to Evaluate the Safety, PK, and Neutralizing Activity of AZD3152 for Pre-exposure Prophylaxis of COVID-19

**Acronym and Brief Title:** SUPERNOVA (Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies) Sub-study

**Study Physician Name and Contact Information will be provided separately**

# SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| CSP Addendum Version 2.0 | 13 June 2023 |
| CSP Addendum Version 1.0 | 22 May 2023 |

## CSP Addendum Version 2.0 [13 June 2023]

### Overall Rationale for the Modification:

Feedback from the FDA was received on CSP Addendum Version 1.0, related to the study population, study assessments, statistical analysis, and description of the sub-study. This amendment to the addendum has been created to address those comments.

### Summary of Changes:

### List of Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page<br>4.1 Overall Design<br>4.2 Scientific Rationale for Study Design | Sub-study classed as Phase II (not Phase III) | FDA recommendation |
| Title Page | Study EudraCT number replaced with IND number | This sub-study will be conducted in the US |
| Synopsis<br>2.1 Study Rationale<br>4.2 Scientific Rationale for Study Design | Updated text to clarify that this sub-study will provide AZD3152 safety data to support a potential indication in treatment of COVID-19 | Clarification |
| Synopsis<br>3 Objectives and Endpoints | Moved the secondary objective to characterize the correlation between predicted nAbs and the change from baseline measured serum nAbs against the relevant SARS-CoV-2 variants with the 1200 mg IV AZD3152 dose to the exploratory objectives | The underlying data for this endpoint is the measured SARS-CoV-2 nAb which is exploratory |
| 1.3 Schedule of Activities | Added weight assessment at Day 29 for immunocompromised participants on the EVUSHELD arm accepting and receiving the offer of 1200 mg IV AZD3152 | To ensure that the participant has a safe weight for receiving study intervention |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities | SARS-CoV-2 testing (local and central laboratories) added at Visit 1 | FDA recommendation |
| | SARS-CoV-2 testing (local laboratory) added at Day 29 for immunocompromised participants on the EVUSHELD arm accepting and receiving the offer of 1200 mg IV AZD3152 | To capture acute SARS-CoV-2 status before dosing participants |
| | Added serum chemistry, hematology, coagulation to screening for the Sentinel Safety Cohort | To ensure there are normal laboratory values for healthy participants |
| 2.3.1 Risk Assessment | Added text regarding the safety data from the first approximately 80 participants in the Main Cohort of the SUPERNOVA Parent study were reviewed by the DSMB | Updated information regarding the status of the DSMB review |
| 4.2 Scientific Rationale for Study Design | Updated text to clarify the primary endpoints of the study | Clarification |
| 4.2.4 Rationale for Use of EVUSHELD as Comparator | Changed section title and modified the text to clarify the rationale for the use of EVUSHELD as a comparator | Clarification |
| 5.1 Inclusion Criteria<br>5.1.1 Sub-study Sentinel Safety Cohort<br>5.1.2 Full Sub-study Cohort<br>5.1.3 Sub-study Sentinel Safety Cohort and Full Sub-study Cohort | Added sub-section headings to clarify the inclusion criteria for the Sub-study Sentinel Safety Cohort and the Full Sub-study Cohort | Clarification |
| 5.1.1 Sub-study Sentinel Safety Cohort<br>5.1.2 Full Sub-study Cohort | Format of inclusion #1 modified | Changes made to ensure criterion can be answered with yes or no |
| 5.1.1 Sub-study Sentinel Safety Cohort | Added Inclusion criterion #2 to specify the age of participants for the Sub-study Sentinel Safety Cohort | Clarification |
| | Added inclusion criterion #3 to specify the weight of participants for the Sub-study Sentinel Safety Cohort | To ensure that the participant has a safe weight for receiving study intervention to confirm eligibility for entry into the study |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1.3 Sub-study Sentinel Safety Cohort and Full Sub-study Cohort | Inclusion criterion #2 added. | Participants must have negative rapid antigen test prior to dosing at Visit 1 |
| 5.2 Exclusion Criteria<br>5.2.1 Sub-study Sentinel Safety Cohort<br>5.2.2 Sub-study Sentinel Safety Cohort and Full Sub-study Cohort | Added sub-sections headings to clarify the inclusion criteria for the Sub-study Sentinel Safety Cohort and the Full Sub-study Cohort | Clarification |
| 5.2.2 Sub-study Sentinel Safety Cohort and Full Sub-study Cohort | Exclusion criterion #10 added | Participants must not have a COVID- 19 vaccine within 3 months prior to Visit 1 |
| | Exclusion criterion #11 added | Participants must not have a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1 |
| | Exclusion criterion #12 added | Participants must not have COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory testing or a rapid test [including at home testing]) |
| 6.5 Concomitant Therapy | Added text to clarify the concomitant therapy for healthy participants and that Table 4 lists the permitted and restricted medications for immunocompromised and immunocompetent (excluding healthy participants) | Clarification |
| 6.5 Concomitant Therapy, Table 9 Permitted, Restricted, and Prohibited Medications | Updated text around routine vaccines | Clarification |
| | Added text to reflect that SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1. SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments | Clarification |
| | Added text to reflect that COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks prior to Visit 1 or during the study until after the Day 29 assessments. If | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | the participant develops COVID-19, standard of care treatment is allowed<br><br>Added text to reflect that receipt of IV or SC immunoglobulin or blood products within 6 months prior to Visit 1 and expected to receive IV or SC immunoglobulin or blood products 6 months after dosing<br><br>Added text to reflect that EVUSHELD should not be given within 12 months prior to dosing with study intervention at Visit 1, and 6 months after dosing with any study intervention | Clarification<br><br>Clarification |
| 1.3 Schedule of Activities<br>8.1.2 Vital Signs | For Sentinel Safety Cohort participants on Day 1, vital signs will be monitored predose and again every 15 minutes for up to 2 hours after IMP administration | FDA recommendation |
| 1.3 Schedule of Activities<br>4.1 Overall Design<br>8.1.5.1 Immediate Adverse Events | For the Sentinel Safety Cohort, on Day 1 the observation period will be extended to 2 hours after study intervention administration | FDA recommendation |
| 1.3 Schedule of Activities<br>8.1.5.2 Injection Site Reaction (IM administrations) and Infusion-related Reactions (IV administration) | The injection site reactions and infusion-related monitoring will be performed 2 hours after dosing is complete on Day 1 for the Sentinel Safety Cohort | FDA recommendation |
| 8.2.1 Time Period and Frequency for Collecting AE and SAE Information | Modified text to specify that "COVID-19, or asymptomatic SARS-CoV-2 infection", should be reported on the AE CRF page | FDA recommendation |
| 8.4.2.3 SARS-CoV-2 Neutralizing Responses | Removed "or authentic virus" for the neutralization assay for the measurement SARS-CoV-2 nAbs | The selected assay is pseudovirus for consistency with other studies |
| 9.1 Statistical Hypotheses | Added more details around the superiority assessment | FDA recommendation |
| 9.4.1 General Considerations | Noted that confidence intervals will be 95% | For consistency with the changes introduced in Section 9.1 |
| 9.4.2 Primary Analysis – Predicted SARS-CoV-2 nAb Response | Added the details on $IC_{50}$ | Details on $IC_{50}$ were removed from general sections for simplicity and are now in |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | | Section 9.4.2 where additional clarification on $IC_{50}$ source is provided |
| 9.5 Planned Analyses | Noted that additional interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor | Clarification |
| Appendix F Definitions for Healthy and Immunocompromised Participants | Added the definition for healthy participants | Clarification |

## List of Non-Substantial Modifications

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>2.1 Study Rationale<br>3 Objectives and Endpoints<br>4.2.1 Rationale for the Primary Endpoint<br>4.3.1 Justification for AZD3152 Dose<br>8.4.1 Pharmacokinetics<br>9 Statistical Considerations | Added text to clarify predicted SARS-CoV-2 nAb responses | For consistency and clarification |
| Synopsis<br>2.1 Study Rationale<br>3 Objectives and Endpoints<br>4.2.1 Rationale for the Primary Endpoint<br>9.4.2 Primary Analysis – Predicted SARS-CoV-2 nAb Response | Added text to clarify in-vitro $IC_{50}$ | Clarification |
| Synopsis<br>2.1 Study Rationale<br>4.2.1 Rationale for the Primary Endpoint | Removed the details on $IC_{50}$ | Details on $IC_{50}$ were removed from general sections for simplicity and kept in Section 9.4.2 where additional clarification on $IC_{50}$ source is provided |
| Synopsis<br>4.1 Overall Design | Added “internal” to clarify a 72-hour internal safety review | Clarification |
| Synopsis | Added text to clarify that the independent DSMB will review safety data in an unblinded manner | For consistency |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis<br>9.4.6 Safety | Added text to clarify that most recent version of MedDRA, where possible, will be used | Clarification |
| 1.3 Schedule of Activities | Specified local laboratory for the troponin T or I assessment | Clarification |
| 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease | COVID-19 statistics updated | Data have been brought up to date |
| 2.2.2 AZD3152 and EVUSHELD<br>2.3.1 Risk Assessment | 'FcRn' amended to 'FcγR' and also noted that AZD3152 expected to reduce potential risk of antibody dependent enhancement of disease (as well as infection) | FDA recommendations |
| Synopsis<br>4.1 Overall Design | Added "approximately" to clarify that the first approximately 12 participants in the sub-study will be healthy volunteers | Clarification |
| Synopsis<br>4.1 Overall Design | Modified wording around the conduct of the Sentinel Safety Cohort and the Full Sub-study Cohort | Reworded for clarity |
| 4.1 Overall Design | Immediate AE observation period has been extended from 1 to 2 hours | FDA recommendation |
| | Modified text to reflect that participants should refrain from receiving SARS-CoV-2 vaccines until after the Day 29 assessments | Consistency with Section 6.5 |
| 6 Study Intervention | Added "(AZD7224)" to "EVUSHELD" | Clarification |
| 6.1 Study Intervention(s) Administered | Added text to see Appendix E for details on the treatment of anaphylactic reactions after study intervention IM injections and IV infusions | Clarification |
| 8.1.1 Physical Examinations | Modified text to reflect that each clinically significant abnormal finding following administration of study intervention should be reported as an AE | For consistency with Section 8.2 |
| 8.1.3 Electrocardiograms | Changed "normal or abnormal" to "normal, borderline, or abnormal" | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.1.4 Clinical Safety Laboratory Assessments | Modified the wording around urine or serum β-hCG pregnancy testing | Reworded for clarity |
| 8.4.1 Pharmacokinetics<br>8.4.2.1 Anti-drug Antibody Assessments | Added "AZD7224" to "(EVUSHELD)" | Clarification |
| 8.4.2.1 Anti-drug Antibody Assessments | Modified text to clarify that samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination, and may also undergo further anti-drug nAbs characterization | Clarification |
| 9 Statistical Considerations | Noted that the planned analyses (and reporting) of the sub-study results will be conducted independently from the SUPERNOVA Parent study | Clarification |

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# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| β-hCG | beta human chorionic gonadotropin |
| CI | Confidence interval |
| COVID-19 | Coronavirus disease 2019 |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trial Information System |
| DES | Data Entry Site |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EU | European Union |
| EUA | Emergency Use Authorization |
| Fc | Fraction crystallizable |
| FcRn | Neonatal Fc receptor |
| FcγR | Fc gamma receptor |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |
| gSD | Geometric standard deviation |
| HIPAA | Health Insurance Portability and Accountability Act |
| HL | Hy's law |
| $IC_{50}$ | Concentration required for 50% inhibition |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |

| Abbreviation or special term | Explanation |
|---|---|
| Ig | Immunoglobulin |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| IV | Intravenous |
| MAAE | Medically attended adverse event |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| nAb | Neutralizing antibody |
| NIMP | Noninvestigational medicinal product |
| PEF | Peak expiratory flow |
| PHL | Potential Hy's law |
| PK | Pharmacokinetics |
| PT | Preferred term |
| QTL | Quality tolerance limit |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RTSM | Randomization and Trial Supply Management |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SC | Subcutaneous |
| SoA | Schedule of activities |
| SOC | System organ class |
| TBL | Total bilirubin |
| TM | L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding |
| ULN | Upper limit of normal |
| US | United States of America |
| VOC | Variant of concern |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |
| YTE | M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase II Open Label Sub-study to Evaluate the Safety, PK, and Neutralizing Activity of AZD3152 for Pre-exposure Prophylaxis of COVID-19

**Rationale:**

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 variants of concern for pre-exposure prophylaxis of COVID-19. AstraZeneca is developing AZD3152 for current or future VOCs and to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

This Phase II sub-study of SUPERNOVA will assess the safety, PK, and predicted neutralizing activity of AZD3152 in adults 18 years of age or older (weighing at least 40 kg) with conditions causing immune impairment who are less likely to mount an adequate protective immune response after vaccination as well as individuals who are immunocompetent (including healthy participants) with all degrees of SARS-CoV-2 infection risk.

This sub-study will bridge the established safety, PK, and neutralizing activity of EVUSHELD™ (AZD7442, comprised of cilgavimab [AZD1061] and tixagevimab [AZD8895], which is approved in major markets worldwide for the pre-exposure prophylaxis of COVID-19) against SARS-CoV-2 Alpha to AZD3152 against SARS-CoV-2 XBB.1.5 (or other circulating VOC), through the demonstration of comparable safety profiles, PK, and predicted SARS-CoV-2 nAb titer responses at Day 29 following study intervention. The predicted SARS-CoV-2 nAb titer for each mAb will be estimated from the serum PK concentration divided by the in-vitro $IC_{50}$ for AZD3152 and Alpha $IC_{50}$ for EVUSHELD. Furthermore, this sub-study will provide AZD3152 safety data to support a potential indication in treatment of COVID-19.

## Objectives and Endpoints

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD3152 and EVUSHELD | Occurrence of AEs collected through 29 days after IMP administration for the primary analysis.<br>SAEs, MAAEs, and AESIs collected throughout the study for the final analysis. |
| To compare the predicted SARS-CoV-2 nAb responses to XBB.1.5 variant (or other circulating VOC) following AZD3152 administration vs predicted SARS-CoV-2 nAb responses to Alpha variant following EVUSHELD administration | **Population**: SARS-CoV-2 PK analysis set<br>**Endpoint**: Predicted SARS-CoV-2 nAb titer derived from serum PK and in-vitro $IC_{50}$ for SARS-CoV-2 variants XBB.1.5 (or other circulating VOC) following AZD3152 administration and Alpha variant following EVUSHELD administration.<br>**Summary measure**: Predicted GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29) for the variant that each IMP is intended to neutralize. |
| **Secondary** | |
| To characterize the PK of AZD3152 and AZD7442 (EVUSHELD) in serum | AZD3152, AZD7442 (EVUSHELD), cilgavimab, and tixagevimab concentration in serum, over time |
| To evaluate the ADA response to AZD3152 and AZD7442 (EVUSHELD) in serum | Incidence of ADA to AZD3152, AZD7442 (EVUSHELD), cilgavimab, and tixagevimab; ADA titers |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; GMT = geometric mean titer; $IC_{50}$ = concentration required for 50% inhibition; IMP = investigational medicinal product; IV = intravenous; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

ADA response to AZD3152 and EVUSHELD will not be included in the primary analysis, and will be reported in the final CSR. For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol.

## Overall Design

This Phase II sub-study of SUPERNOVA will evaluate the safety, PK, and neutralizing activity of AZD3152 compared with EVUSHELD for pre-exposure prophylaxis of COVID-19.

This sub-study will enroll approximately 450 participants, ≥ 18 years of age with a minimum weight of 40 kg. An initial Sentinel Safety Cohort will include 12 healthy volunteers; all other participants in the study will be either immunocompromised or immunocompetent (including healthy participants) with all degrees of SARS-CoV-2 infection risk. Recruitment into the sub-study is fully independent from the SUPERNOVA main study.

Participants will be randomized 2:1 to receive AZD3152 1200 mg IV or EVUSHELD 300 mg IM on Day 1. For EVUSHELD, cilgavimab should be administered first followed by tixagevimab.

The first approximately 12 participants in the sub-study will be healthy volunteers and will be enrolled as a Sentinel Safety Cohort with at least 8 participants dosed with AZD3152 and 4 dosed with EVUSHELD. Dosing within the Sentinel Safety Cohort will be staggered, starting with 6 participants, followed by another set of 6 participants, with a 72-hour internal safety review period after each group of participants is enrolled; there will be a rolling safety review period after both sets of 6 participants are enrolled, during which times further dosing will be paused.

After the 72-hour internal safety review for all 12 healthy participants in the Sentinel Safety Cohort, enrollment will continue and participants who are either immunocompromised or immunocompetent (including healthy participants) will be randomized to the AZD3152 or EVUSHELD arm if there are no safety signals that warrant a temporary hold after the final 72-hour internal safety review period. The Sentinel Safety Cohort participants will count towards the Visit 3 analysis.

**Disclosure Statement:**

This is a parallel group, single-dose, open label, safety, PK, and SARS-CoV-2 nAb study.

**Number of Participants:**

Approximately 450 participants, ≥ 18 years of age, will be randomized 2:1 in the study to receive AZD3152 or EVUSHELD.

**Intervention Groups and Duration:**

One dose of AZD3152 1200 mg IV or one dose of EVUSHELD 300 mg IM (× 2 injections, 1 × 150 mg dose of each component). After the Day 29 assessments have been completed for the primary analysis, those immunocompromised participants who received EVUSHELD will be offered the option of receiving AZD3152 as a 1200 mg IV dose.

The duration of each participant's involvement in the study will be approximately 15 months.

**Data Safety Monitoring Board:**

An independent DSMB will meet periodically, review safety data in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will have not been subject to validation and database lock.

**Statistical Methods**

Participant's data will be presented by the dosing regimen received.

Categorical variables will be summarized using frequency and percentages. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles, where more appropriate. Point estimates will be presented with a 95% CI, and reported p-values will correspond to a 2-sided test unless otherwise stated.

The primary analysis will take place after all study participants complete Visit 3 (Day 29) or have withdrawn from the study. The final analysis will take place after the end-of-study visit. The Day 29 primary analysis will present available safety, PK, and predicted SARS-CoV-2 nAb data to evaluate the primary objectives of the study. The final analysis will include all available data collected through the follow-up period of 15 months from Day 1.

The planned analyses (and reporting) of the sub-study results will be conducted independently from the SUPERNOVA Parent study.

*Primary Objectives*

Predicted SARS-CoV-2 nAb Response

Predicted Day 29 SARS-CoV-2 nAb titers will be derived from serum PK and in-vitro $IC_{50}$ for each participant and compared between treatment groups using the GMT ratio. Additional sensitivity analysis will explore other relevant prognostic factors.

A noninferiority comparison will be performed using the ratio of predicted SARS-CoV-2 nAb GMTs (GMTR) at Visit 3 (Day 29) of the XBB.1.5 variant (or other circulating VOC) for participants receiving AZD3152 versus the alpha variant for participants receiving EVUSHELD with a comparability threshold of 0.8, ie, non-inferiority will be concluded if the 2-sided 90% CI for the GMTR is > 0.8.

Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, where possible, and will be summarized by SOC and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on

data type (continuous, categorical, etc).

*Secondary Objectives*

Characterization of PK

Following initial dosing with AZD3152 or EVUSHELD, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group over time.

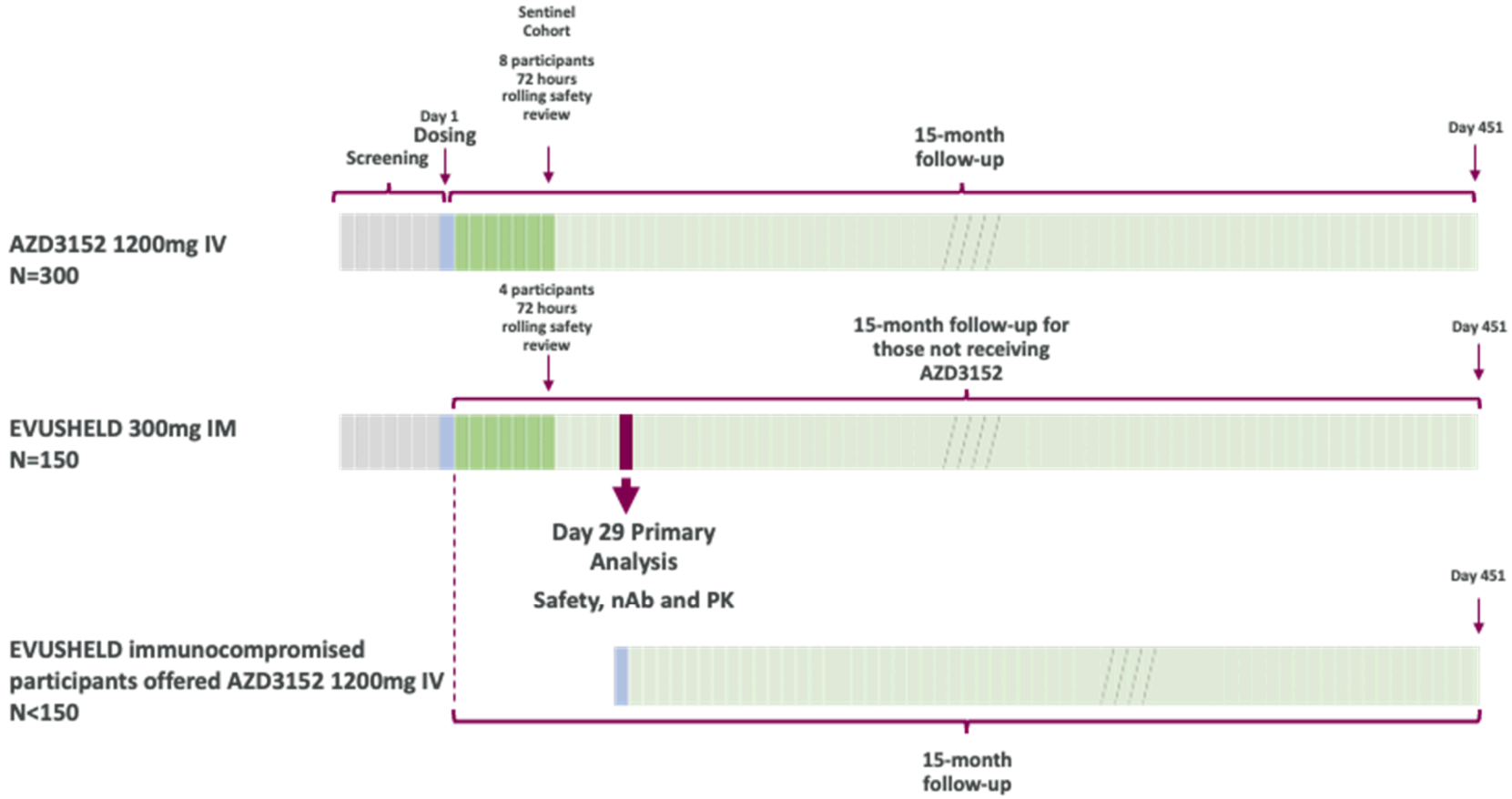
Evaluation of the ADA response.

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set for each mAb or combination of mAbs. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs) and PK will be assessed.

## 1.2 Schema

The study groups and overall study design are described in Figure 1.

**Figure 1 Study Design**




Note: EVUSHELD = AZD1061 (cilgavimab) + AZD8895 (tixagevimab)
IM = intramuscular; IV = intravenous; N = number of participants; nAb = neutralizing antibody; PK = pharmacokinetics.

## 1.3 Schedule of Activities

There will be a screening period of up to 15 days (Day -14 through Day 1), with the treatment and follow-up period lasting 15 months (Table 1).

## Table 1 Schedule of Activities

| Procedure | | Treatment and Follow-up Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2** | **3** | **3a [a]** | **3b [a, b]** | **4** | **5** | **6 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **2** | **2** | **3** | **6** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **29** | **36** | **58** | **91** | **181** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **± 15** | **NA** |
| Written informed consent | X | | | | | | | | | |
| Verify eligibility criteria | X | X (predose) | | | | | | | | |
| Randomization | | X (predose) | | | | | | | | |
| Medical history and demographics | X | | | | | | | | | |
| Full physical examination, including height and weight | X | | | Weight only (predose) [a] | | | | | | X [c] |
| Targeted physical examination based on medical history | | X (predose) | | | | | | | | |
| Vital signs [d] | X | X | X | X [a] | X [a] | | | | | |
| 12-lead electrocardiogram (single, to be performed locally) [e] | X | | | | | | | | | |
| Serum β-hCG (local laboratory) or urine pregnancy test (WOCBP only) [f] | X | X (predose) | | X (predose [a]) | | | | | | |
| Rapid antigen test for SARS-CoV-2 (performed locally) [g] | | X (predose) | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (central laboratory) [h] | | X (predose) | | | | | | | | |
| NP swab for SARS-CoV-2 RT-PCR (local laboratory) [h] | | | | X (predose) [a] | | | | | | |

## Table 1 Schedule of Activities

| Procedure | | Treatment and Follow-up Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2** | **3** | **3a [a]** | **3b [a, b]** | **4** | **5** | **6 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **2** | **2** | **3** | **6** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **29** | **36** | **58** | **91** | **181** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **± 15** | **NA** |
| Serum chemistry, hematology, coagulation (local laboratory) | X [i] | X (predose) | X | X (predose [j]) | | | | | | |
| Troponin T or I (local laboratory) | X | | | | | | | | | |
| Follicle stimulating hormone [k] | X | | | | | | | | | |
| Telephone/email/text contacts-monitoring for safety | | X (weekly until Day 181; monthly thereafter) | | | | | | | | |
| Assessment of AEs | | X (up to Day 29) | | | X [a] (up to Day 58) | | | | | |
| Assessment of SAEs, MAAEs, and AESIs | X (SAEs) | X (ongoing observation and questioning) | | | | | | | | |
| Concomitant medications | X | X (ongoing observation and questioning) | | | | | | | | |
| SARS-CoV-2 serology (anti-nucleocapsid) serum sample | | X (predose) | | X (predose [j]) | | | X | X | | X |
| PK serum sample | | X (predose) | | X (predose [j]) | | | X | X | | |
| ADA and antidrug nAbs assessment serum sample | | X (predose) | | X (predose [j]) | | | X | X | | |
| SARS-CoV-2 nAb serum sample | | X (predose) | | X (predose [j]) | | | X | X | | X |
| Exploratory analysis serum sample | | X (predose) | | X (predose [j]) | | | X | X | | X |
| **Study intervention administration** | | X | | | | | | | | |

## Table 1 Schedule of Activities

| Procedure | | Treatment and Follow-up Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2** | **3** | **3a [a]** | **3b [a, b]** | **4** | **5** | **6 [b]** | **EDV** |
| **Month** | **NA** | **1** | **1** | **1** | **2** | **2** | **3** | **6** | **15** | |
| **Day** | **-14 to 1** | **1** | **8** | **29** | **36** | **58** | **91** | **181** | **451** | **NA** |
| **Window (days)** | **NA** | **NA** | **+ 3** | **+ 3** | **+ 3** | **+ 3** | **± 5** | **+ 4** | **± 15** | **NA** |
| AZD3152 infusion for EVUSHELD recipients (Optional) [l] | | | | X [l] | | | | | | |
| Infusion/Injection site reaction monitoring | | X [m] | X | X [a, m] | X [a] | | | | | |
| Immediate AEs [n] | | X | | X [a] | | | | | | |

[a] Only for immunocompromised participants on the EVUSHELD arm accepting and receiving the offer of 1200 mg IV AZD3152.
[b] Visit will be conducted via telephone call.
[c] Excludes height measurement.
[d] For Sentinel Safety Cohort participants on Day 1, vital signs will be monitored predose and again every 15 minutes for up to 2 hours after IMP administration. On Day 1 for the Full Sub-study Cohort, vital signs will be performed predose and again 10 to 15 minutes after all IMP infusion/injections are given. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[e] The Investigator may add additional ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason (see Section 8.1.3 for additional detail).
[f] Sample urine or serum β-hCG pregnancy test must return a negative result before dosing. Pregnancy testing must be on the same day as dosing.
[g] Sites will be provided with rapid antigen tests where needed.
[h] To be collected before dosing; the results are not needed prior to dosing.
[i] Only for the Sentinel Safety Cohort.
[j] Collected for all participants on Day 29; for those on the EVUSHELD arm accepting and receiving the offer of 1200 mg IV AZD3152, all assessments must be collected predose.
[k] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal.
[l] Immunocompromised participants who received EVUSHELD at Visit 1 may be offered a single dose of AZD3152 IV at Day 29 after all Day 29 assessments have been completed. Refer to Appendix F for the definition for immunocompromised participants for further guidance on those that qualify for the optional AZD3152 dose.
[m] Perform immediately, 30 minutes (+ 10 minutes) and 2 hours after dosing is complete on Day 1 (Sentinel Safety Cohort), 1 hour after dosing is complete (Full Sub-study Cohort) and prior to participant release.
[n] Immediate AEs will be collected for a 2-hour observation period (Sentinel Safety Cohort) or a 1-hour observation period after study intervention administration (Full Sub-study Cohort) on Day 1.

β-hCG = beta human chorionic gonadotropin; ADA = antidrug antibody; AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; IMP = investigational medicinal product; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

# 2 INTRODUCTION

## 2.1 Study Rationale

AZD3152, a single mAb, is being developed to have broad neutralizing activity across known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19 and for treatment of mild to moderate COVID-19 in immunocompromised individuals. AstraZeneca is developing AZD3152 for current VOCs and to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve.

This Phase II sub-study of SUPERNOVA will assess the safety, PK, and predicted neutralizing activity of AZD3152 in adults ≥ 18 years of age (weighing at least 40 kg) with conditions causing immune impairment as well as immunocompetent individuals (including healthy participants) with all degrees of SARS-CoV-2 infection risk.

This sub-study will bridge the established safety, PK, and neutralizing activity of EVUSHELD (AZD1061 [cilgavimab] and AZD8895 [tixagevimab], approved as EVUSHELD™ in major markets worldwide for the pre-exposure prophylaxis of COVID-19) against SARS-CoV-2 Alpha to AZD3152 against XBB.1.5 (or other circulating VOC), through the demonstration of comparable safety profiles, PK, and predicted SARS-CoV-2 nAb titer responses at Day 29 following study intervention. The predicted nAb titer for each mAb will be estimated from the serum PK concentration divided by the in-vitro $IC_{50}$ for AZD3152 and Alpha $IC_{50}$ for EVUSHELD. Furthermore, this sub-study will provide AZD3152 safety data to support a potential indication in treatment of COVID-19.

## 2.2 Background

### 2.2.1 Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Disease

Coronavirus SARS-CoV-2 is the causative agent of COVID-19 and, as of 31 May 2023, has caused over 767 million confirmed cases of COVID-19, including more than 6.9 million deaths, reported to the WHO (WHO 2023). The majority of coronaviruses cause mild disease in humans and animals; however, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia.

In December 2020, a global vaccination campaign was initiated to protect against serious disease associated with COVID-19. Despite the rollout of effective vaccines, which have significantly reduced the morbidity and mortality associated with SARS-CoV-2 infection, there still remains an unmet medical need for individuals who remain at risk of severe and fatal COVID-19 due to their inability to mount an adequate response to complete active immunization (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. Although 2% to 3% of the US population is immunocompromised, a disproportionately larger percentage (17.3%) of patients hospitalized

during the Omicron-period were immunocompromised (Singson et al 2022). At this time, there are no approved mAbs for pre-exposure prophylaxis for the immunocompromised population globally. Thus, this high-risk population would benefit from the development of new mAbs that can prevent COVID-19.

Neutralizing mAbs were developed and deployed to protect those unable to mount an immune response to vaccination. Such antibodies act by inhibiting the ability of SARS-CoV-2 to enter host cells. Coronavirus entry into host cells is mediated by the SARS-CoV-2 spike protein, which forms homotrimers protruding from the viral surface (Hoffmann et al 2020, Walls et al 2017). The SARS-CoV-2 spike protein comprises 2 functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit). The distal S1 subunit comprises the receptor binding domain and contributes to stabilization of the prefusion state of the membrane anchored S2 subunit, which contains the fusion machinery (Bosch et al 2003, Li 2016). The SARS-CoV-2 spike protein is the sole viral membrane protein responsible for cell entry. It binds to the cellular receptor human angiotensin-converting enzyme 2 (ACE-2) on the target cell and mediates virus-cell fusion, allowing the viral genome to enter and replicate in the cell. The SARS-CoV-2 spike protein is surface-exposed and mAbs act through direct targeting of the spike protein. Clinical studies have shown that mAbs that neutralize the spike protein are efficacious in both the prophylaxis and treatment settings.

There is a continued need for additional tools to combat COVID-19 due to the emergence of new SARS-CoV-2 variants with spike proteins containing amino acid substitutions that have reduced the neutralizing potency of the mAbs. This has necessitated continued development of novel antibodies that retain neutralizing functionality against VOCs.

### 2.2.2 AZD3152 and EVUSHELD

The SARS-CoV-2 virus has demonstrated its ability to evolve and generate VOCs that can decrease or eliminate the efficacy of existing mAb therapies, including EVUSHELD. The potency of EVUSHELD was reduced with the emergence of the Omicron lineage, especially the BA.1, BA.1.1, and more recently the XBB Omicron lineages (Case et al 2022; Lusvarghi et al 2022). Neutralizing potency was regained against some of the more recent Omicron variants (Tuekprakhon et al 2022); however, the loss of potency against BA.1, BA.1.1, and XBB.1.5 highlighted the need for development of additional antibodies. A prophylactic product for the prevention of symptomatic COVID-19 that neutralizes all known SARS-CoV-2 viral variants would provide an additional option to help minimize individual risk, minimize outbreaks, and control the spread of disease in the ongoing pandemic. AZD3152 is being developed to provide efficacy similar to that of EVUSHELD but with greater breadth against variants not potently neutralized by EVUSHELD.

AZD3152 is a novel mAb chosen based on its improved breadth of coverage against Omicron

variants compared to EVUSHELD, specifically high neutralizing potency against all the current Omicron variants.

AZD3152 has been engineered with the YTE (M257Y/S259T/T261E [Dall'Acqua et al 2006]) substitution to extend the mAb half-life, and the TM (L234F/L235E/P331S [Oganesyan et al 2008, Loo et al 2022]) substitution to reduce effector function through reduced human FcγR or complement component 1q (C1q) binding, which is expected to reduce potential risk of antibody dependent enhancement of infection or disease. Incorporation of these amino acid substitutions did not alter the neutralization potency of EVUSHELD in vitro. Given both AZD3152 and EVUSHELD target the SARS-CoV-2 spike protein and have the YTE and TM substitutions, the clinical development program for AZD3152 builds upon the established safety and efficacy of EVUSHELD. AZD3152 is expected to have a similar safety and PK profile and broader efficacy against a wider range of SARS-CoV-2 VOCs than EVUSHELD.

It is considered reasonable that AZD3152 will be effective for pre-exposure prophylaxis of COVID-19 for the following reasons:

- The mechanism of action and PK of AZD3152 are similar to those of the component mAbs of EVUSHELD.
- In vitro pseudovirus neutralization data demonstrates that AZD3152 neutralizes all variants of concern, including Omicron variants BA.1, BA.1.1, BA.4/5, BQ.1, BQ.1.1, BF.7, XBB, XBB.1, XBB.1.5, and XBB.1.16.
- EVUSHELD has demonstrated efficacy in reducing the incidence of symptomatic COVID-19 compared with placebo in the PROVENT (D8850C00002/NCT04625725) study (Levin et al 2022) and is approved as EVUSHELD in major markets for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the EU and Japan.

Individuals who may most benefit from protection against COVID-19 with AZD3152 include individuals who are not expected to mount an adequate or long lasting immune response to complete SARS-CoV-2 vaccination (eg, individuals with immunocompromising conditions including those taking immunosuppressive medications for rheumatologic diseases, myeloablative chemotherapy for solid and hematologic malignancies, stem and solid organ transplant recipients and those with primary immunodeficiency syndromes) or for whom vaccination is not suitable.

A detailed description of the chemistry, pharmacology, and nonclinical studies of AZD3152 are provided in the Investigator's Brochure.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

As with EVUSHELD, AZD3152 is a human IgG1 mAb directed against the receptor binding domain of the SARS-CoV-2 S protein for neutralization of the virus. AZD3152 does not have any known endogenous human target. There are no identified risks for AZD3152 as no clinical data are currently available. Early Safety Data Review Committee reviews of Day 8 and Day 15 data from the Sentinel Cohort of the SUPERNOVA parent study are now complete and no safety concerns were identified. The safety data from the first approximately 80 participants in the Main Cohort were reviewed by the DSMB and no safety concerns were noted, which allowed the opening of enrollment of adolescents into the main study. Overall, the structural similarities between AZD3152 and EVUSHELD suggest the anticipated safety profile of AZD3152 is expected to be similar to the observed safety profile of EVUSHELD; modifications made for AZD3152 are not expected to have an effect on safety.

The potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs, include injection site reactions, infusion-related reactions, anaphylaxis, and other serious hypersensitivity reactions including immune complex disease, and antibody dependent enhancement of infection.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection. Clinical studies with AZD3152 will closely monitor participants during and after study intervention administration. These reactions should be managed according to standard clinical practice.

Monoclonal antibodies have the potential to cause anaphylaxis and other hypersensitivity reactions including immune complex disease, which could induce the development of ADAs. The occurrence of such ADAs could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered AZD3152 levels or activity. Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies.

An infusion-related reaction is defined as any other reaction (other than hypersensitivity and anaphylaxis) occurring during infusion of study intervention or felt to be temporarily related to the infusion and occurring within 30 minutes to 2 hours after the initiation of first study intervention infusion. However, though less frequent, infusion-related reactions can also occur later on within the first 24 hours from the start of infusion and are less common following subsequent exposures. Infusion-related reactions may manifest with single or multiple signs and symptoms. Most are mild in intensity, but severe and even fatal reactions have been reported. Unlike infusion-related reaction, anaphylaxis is a rare event, usually occurring after

subsequent exposure to an antigen, and is most commonly accompanied by severe systemic skin and/or mucosal reactions.

For all mAbs, antibody dependent enhancement of infection is a theoretical risk and has not been seen in the currently available mAbs to prevent or treat COVID-19. One of the syndromes of antibody dependent enhancement of infection involves increased binding efficiency of virus-antibody complexes to FcR-bearing cells and which triggers virus entry. This is not expected with AZD3152 because, similar to EVUSHELD, they have been designed with a modification to prevent binding to cellular Fc receptors, thus significantly lowering the risk of antibody dependent enhancement of infection or disease occurring via this mechanism.

In the pre-exposure prophylaxis study PROVENT (D8850C00002) within the EVUSHELD program, there was a numerical imbalance in SAEs in the Cardiac disorders SOC between AZD7422 and placebo (1.2% versus 0.5%). SAEs with PTs under the Cardiac disorder SOC or the standardized MedDRA query 'embolic and thrombotic events' (cardiac and thromboembolic SAEs) were reported by 1.6% of participants in the EVUSHELD group and 0.9% of participants in the placebo group. In total, 5197 participants were dosed with IMP during the study (3461 with EVUSHELD and 1736 with placebo), randomized at a 2:1 ratio to EVUSHELD or placebo, respectively. The incidence of serious adverse events (SAEs) was 6.2% of participants for EVUSHELD versus 5.6% for placebo. There was no clear temporal pattern, and all participants who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of cardiovascular disease at baseline. Furthermore, no clinically meaningful imbalances were observed for cardiac events in other EVUSHELD clinical studies, including placebo-controlled studies TACKLE (D8851C00001) and STORM CHASER (D8850C00003). There are no endogenous human targets for EVUSHELD that have been corroborated by tissue cross-reactivity analysis. Overall, a causal relationship between EVUSHELD and cardiac events has not been established.

### 2.3.2 Benefit Assessment

AZD3152 may be efficacious and offer participants protection from COVID-19. AZD3152 is similar (structurally and in terms of mechanism of action) to EVUSHELD which demonstrated an 83% reduced risk of developing symptomatic COVID-19 at 6 months compared with placebo in participants who were SARS-CoV-2 negative at baseline, as shown in the Phase III PROVENT trial (Levin et al 2022). It should be noted that the comparator EVUSHELD, as well as AZD3152, may be ineffective against current and/or future VOCs of the SARS-CoV-2 virus.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate or long lasting immune response to complete active immunization (CDC 2021), and those for whom

vaccination is not suitable.

The individuals to be included in this study are adults ≥ 18 years old who have a condition causing immune impairment, the proposed indicated population, as well as immunocompetent individuals (including healthy participants) with all degrees of SARS-CoV-2 infection risk.

### 2.3.3 Overall Benefit: Risk Conclusion

Overall, it is considered that the AZD3152 nonclinical data available to date, together with the safety data available from the Sentinel Cohort in the parent study, as well as clinical data from similar mAbs, including EVUSHELD, provide confidence that the overall benefit-risk is favorable.

Detailed information about the known and expected benefits and potential risks of AZD3152 and EVUSHELD is provided in the respective Investigator's Brochures.

# 3 OBJECTIVES AND ENDPOINTS

**Table 2 Objectives and Endpoints**

| Objectives | Estimand Description/Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety of AZD3152 and EVUSHELD | Occurrence of AEs collected through 29 days after IMP administration for the primary analysis.<br>SAEs, MAAEs, and AESIs collected throughout the study for the final analysis. |
| To compare the predicted SARS-CoV-2 nAb responses to XBB.1.5 variant (or other circulating VOC) following AZD3152 administration vs predicted SARS-CoV-2 nAb responses to Alpha variant following EVUSHELD administration | **Population**: SARS-CoV-2 PK analysis set<br>**Endpoint**: Predicted SARS-CoV-2 nAb titer derived from serum PK and in-vitro $IC_{50}$ for SARS-CoV-2 variants XBB.1.5 (or other circulating VOC) following AZD3152 administration and Alpha variant following EVUSHELD administration.<br>**Summary measure**: Predicted GMT ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29) for the variant that each IMP is intended to neutralize. |
| **Secondary** | |
| To characterize the PK of AZD3152 and AZD7442 (EVUSHELD) in serum | AZD3152, AZD7442 (EVUSHELD), cilgavimab, and tixagevimab concentrations in serum, over time |
| To evaluate the ADA response to AZD3152 and AZD7442 (EVUSHELD) in serum | Incidence of ADA to AZD3152, AZD7442 (EVUSHELD), cilgavimab, and tixagevimab; ADA titers |

| **Exploratory** | |
|---|---|
| To determine anti-SARS-CoV-2 nAb levels in serum following a single IV dose of IMP | Descriptive baseline and post-treatment nAb GMTs |
| To characterize the correlation between predicted SARS-CoV-2 nAbs and the change from baseline measured serum nAbs against the relevant SARS-CoV-2 variants with the 1200 mg IV AZD3152 dose | Descriptive correlation statistics |
| To assess additional immune responses in participants administered EVUSHELD and AZD3152 | Other exploratory assays for humoral, and immune responses may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data |

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; GMT = geometric mean titer; $IC_{50}$ = concentration required for 50% inhibition; IMP = investigational medicinal product; IV = intravenous; MAAE = medically attended adverse event; nAb = neutralizing antibody; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

ADA response to AZD3152 and EVUSHELD will not be included in the primary analysis, and will be reported in the final CSR. Exploratory endpoints may not be included in the primary analysis and may be reported separately from the CSR.

# 4 STUDY DESIGN

## 4.1 Overall Design

This Phase II sub-study of SUPERNOVA will evaluate the safety, PK, and neutralizing activity of AZD3152 compared with EVUSHELD for pre-exposure prophylaxis of COVID-19. This sub-study will be conducted in the US.

This sub-study will enroll approximately 450 participants, ≥ 18 years of age with a minimum weight of 40 kg. An initial Sentinel Safety Cohort will include 12 healthy volunteers; all other participants in the study will be either immunocompromised or immunocompetent (including healthy participants) with all degrees of SARS-CoV-2 infection risk, in order to maximize recruitment potential. The definitions for immunocompromised and healthy participants are listed in Appendix F.

Participants will be randomized 2:1 to receive AZD3152 1200 mg IV or EVUSHELD (AZD1061 [cilgavimab] and AZD8895 [tixagevimab]) 300 mg IM on Day 1. For EVUSHELD, cilgavimab should be administered first followed by tixagevimab.

The first approximately 12 participants in the sub-study will be healthy volunteers and will be

enrolled as a Sentinel Safety Cohort with at least 8 participants dosed with AZD3152 and 4 dosed with EVUSHELD. Dosing within the Sentinel Safety Cohort will be staggered, starting with 6 participants, followed by another set of 6 participants, with a 72-hour internal safety review period after each group of participants is enrolled; there will be a rolling safety review period after both sets of 6 participants are enrolled, during which times further enrollment will be paused.

After the 72-hour internal safety review for all 12 healthy participants in the Sentinel Safety Cohort, enrollment will continue and participants who are either immunocompromised or immunocompetent (including healthy participants) will be randomized to the AZD3152 or EVUSHELD arm if there are no safety signals that warrant a temporary hold after the final 72-hour internal safety review period. The Sentinel Safety Cohort participants will count towards the Visit 3 analysis.

After the Day 29 assessments have been completed for the primary analysis, those immunocompromised participants who received EVUSHELD will be offered the option of receiving AZD3152 as a 1200 mg IV dose.

The duration of each participant's involvement in the study will be approximately 15 months.

Adverse events will be collected in the eCRF for 28 days after dosing. Serious adverse events, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for a 2-hour observation period (Sentinel Safety Cohort) or a 1-hour observation period after study intervention administration (Full Sub-study Cohort) on Day 1.

Participants should refrain from receiving SARS-CoV-2 vaccines until after the Day 29 assessments.

The study groups and overall study design are described in Figure 1.

Planned analyses are discussed in Section 9.5.

### 4.1.1 Safety Review

The safety data collected will be entered into eCRFs and reviewed on an ongoing basis. These reviews will be based on preliminary data that will not have been subject to validation and database lock.

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the sub-study, as discussed in Section 9.6.

## 4.2 Scientific Rationale for Study Design

This is a Phase II sub-study and an addendum to the Phase III SUPERNOVA study. The

primary endpoints are standard safety assessments and the predicted GMT of SARS-CoV-2 XBB.1.5 variant (or other circulating VOC) nAbs (following AZD3152 administration) and predicted GMT of Alpha variant nAbs (following EVUSHELD administration). A separate dose exploration study (D7000C00004; Little DIPPER) will be conducted to evaluate the safety and pharmacokinetics of AZD3152 300 mg and 600 mg administered by IV and by IM route. Furthermore, this sub-study will provide AZD3152 safety data to support a potential indication in treatment of COVID-19.

Participants in the sub-study will be randomized 2:1 to AZD3152 1200 mg IV or EVUSHELD 300 mg IM. Based on evaluation of available in vitro neutralization data and the current landscape of circulating variants, together with recognition of Agency feedback to consider continuing development with AZD3152 at higher doses, AstraZeneca has initiated this sub-study using AZD3152 at a 1200 mg IV dose to compare against EVUSHELD 300 mg IM.

### 4.2.1 Rationale for the Primary Endpoint

The primary endpoint is a comparison of the predicted SARS-CoV-2 nAb responses to XBB.1.5 variant (or other circulating VOC) following AZD3152 administration vs the predicted nAb responses to Alpha variant following EVUSHELD administration. The predicted nAb titer for each mAb will be estimated from the serum PK concentration divided by the in-vitro $IC_{50}$ for AZD3152 and Alpha $IC_{50}$ for EVUSHELD.

AZD3152 1200 mg IV dose was selected to provide predicted SARS-CoV-2 nAb titers against XBB.1.5 (or other circulating VOC) comparable to EVUSHELD 300 mg IM against Alpha through 6 months based upon data from the PROVENT study.

Using predicted nAb titers reduces the possible imbalance due to any baseline nAb titers, which are expected to be higher for Alpha vs XBB.1.5 (or other circulating VOC), considering vaccinations and previous exposure to SARS-CoV-2 in trial participants. Using predicted nAb titers allows enrollment of both immunocompromised and immunocompetent participants (including healthy participants), that likely have differences in baseline nAb levels related to vaccinations and SARS-CoV-2 exposure, into the sub-study.

### 4.2.2 Rationale for Administration Site

Participants will receive AZD3152 as an IV infusion or EVUSHELD as an IM injection in the gluteal region. EVUSHELD will be administered as 2 sequential IM injections, one injection for each component, with the second injection administered in the contralateral side to limit the injection volume into the muscle to reduce the risk of local site reactions.

The clinical studies that supported the EUA for EVUSHELD in the US, and the marketing authorization application in the EU, administered EVUSHELD by IM in the gluteal region. EVUSHELD will be administered by IM in the gluteal region for this sub-study to match the

site of administration from the PROVENT study, as this sub-study will bridge to PROVENT data.

Intravenous administration of AZD3152 was selected to reduce the number of injections of IMP needed for an IM administration for the larger dose.

### 4.2.3 Rationale for Study Population

This sub-study will be conducted in adults ≥ 18 years of age with conditions causing immune impairment (ie, the current population being enrolled in the parent study SUPERNOVA) as well as individuals who are immunocompetent (including healthy participants) with all degrees of SARS-CoV-2 infection risk. The broad study population has been selected to reflect real word populations that may benefit from AZD3152.

### 4.2.4 Rationale for Use of EVUSHELD as Comparator

Despite the current decline in neutralizing activity of EVUSHELD against currently circulating variants, AstraZeneca considers EVUSHELD 300 mg an appropriate comparator for bridging. The 300 mg IM dose matches that used in PROVENT D8850C00002, allowing for bridging to the PROVENT efficacy data as suggested by the FDA. In this sub-study, participants will receive mAbs whose safety profile is expected to be very similar, and immunocompromised participants who receive EVUSHELD as a first dose will be given the option to receive AZD3152 on Day 29 after completion of all Day 29 assessments.

## 4.3 Justification for Dose

### 4.3.1 Justification for AZD3152 Dose

AZD3152 1200 mg IV will be used as the dose in the study. A 1200 mg IV dose of AZD3152 was selected to provide:

- Comparable predicted SARS-CoV-2 nAb titer on Day 29 against the XBB.1.5 variant (or other circulating VOC) to EVUSHELD 300 mg IM against the Alpha variant (higher predicted nAb titer for AZD3152 prior to Day 29)
- Consistent duration of protection (6 months) with EVUSHELD 300 mg IM against the Alpha variant

### 4.3.2 Justification for EVUSHELD Dose

The 300 mg IM dose matches that used in PROVENT D8850C00002, allowing for bridging to the PROVENT efficacy data.

## 4.4 End of Study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs

under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Table 1).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Table 1) for the last participant in the study globally.

The results from some laboratory samples may not become available until after the study completion date.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 Inclusion Criteria

Participants are eligible to be included in this sub-study only if all of the following criteria apply:

### 5.1.1 Sub-study Sentinel Safety Cohort

1 Healthy, defined according to medical history, physical examination, baseline safety laboratory tests, and screening parameters, according to the judgment of the Investigator.

2 Participants must be 18 to 55 years at the time of signing the informed consent.

3 Weight ≥ 45 kg and ≤ 110 kg at screening.

### 5.1.2 Full Sub-study Cohort

1 Immunocompromised (refer to Appendix F for the definition for immunocompromised participants) or immunocompetent, including healthy participants, with all degrees of SARS-CoV-2 infection risk, will be enrolled following completion of Sentinel Safety Cohort enrolment.

2 Participants must be 18 years of age or older at the time of signing the informed consent.

3 Weight ≥ 40 kg at screening.

### 5.1.3 Sub-study Sentinel Safety Cohort and Full Sub-study Cohort

1 Written informed consent and any locally required authorization (eg, HIPAA in the US) obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.

2 Negative rapid antigen test for SARS-CoV-2 prior to dosing at Visit 1.

3 Medically stable defined as disease not requiring significant change in maintenance therapy or hospitalization for worsening disease or any recent cardiovascular event (eg, acute myocardial infarction, thromboembolic event) during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator and no expected changes at the time of the enrollment.

4 Able to understand and comply with all study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined), based on the assessment of the Investigator.

## 5.2 Exclusion Criteria

Participants are excluded from this sub-study if any of the following criteria apply:

### 5.2.1 Sub-study Sentinel Safety Cohort

1 Active infection with hepatitis B or C.

2 Serum creatinine, AST, or ALT above 1.5 × ULN at screening.

3 History of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years.

### 5.2.2 Sub-study Sentinel Safety Cohort and Full Sub-study Cohort

1 Receipt of EVUSHELD (AZD7442) within 12 months prior to Visit 1.

2 Women who are pregnant, lactating, or of childbearing potential and not using a highly effective method of contraception or abstinence from at least 4 weeks prior to study

intervention administration and until at least 6 months after study intervention administration.

(a) Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
- Females ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

(b) Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Females of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 6 months after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician.

(c) The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea. Female condom and male condom should not be used together.

(d) All female participants of childbearing potential must have a negative urine or serum (β-hCG) pregnancy test result at screening and Visit 1.

(e) Highly effective birth control methods include: Total sexual abstinence, provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments [periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal are not acceptable methods of contraception]), a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®.

3 Known hypersensitivity to any component of the study intervention.

4 Previous hypersensitivity or severe adverse reaction following administration of a mAb.

5 Acute (time-limited) or febrile (temperature ≥ 38.0°C [100.4ºF]) illness/infection on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves and may be rescreened for enrollment once.

6 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to Visit 1.

7 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture.

8 Has human immunodeficiency virus infection.

9 Receipt of IV or SC immunoglobulin or blood products within 6 months prior to Visit 1 and expected to receive IV or SC immunoglobulin or blood products 6 months after dosing.

10 Receipt of a COVID-19 vaccine within 3 months prior to Visit 1.

11 Receipt of a COVID-19 antiviral for prophylaxis within at least 2 weeks prior to Visit 1.

12 COVID-19 within 3 months prior to Visit 1 (confirmed either by laboratory RT-PCR testing or a rapid antigen test [including at-home testing]).

13 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study (except where the participant ceased IMP treatment > 90 days and is in the follow-up period of the study and not expected to receive further IMP).

14 Alcohol or substance abuse that, in the opinion of the Investigator, might interfere with the trial conduct or completion.

15 Deprived of freedom by an administrative or court order, or in emergency setting, or hospitalized involuntarily.

16 Any condition that, in the opinion of the Investigator, might compromise participant safety or interfere with evaluation of the study intervention or interpretation of participant safety or study results.

17 Employees of AstraZeneca involved in planning, executing, supervising, or reviewing the AZD3152 program, clinical study site staff, or any other individuals involved with the conduct of the study, or family members of such individuals.

## 5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Section 5.2.
- Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but

are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure or unforeseen personal events that mandate missed screening visit). Only a single rescreening is allowed in the study, which can occur at any time during the enrollment period. When possible, the Investigator should consult the Study Physician prior to rescreening. Rescreened participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

Participants will be randomized (2:1 ratio) to receive AZD3152 or EVUSHELD (AZD7442). Details of these study interventions are presented in Table 3 and are described below.

Administration of AZD3152 will comprise of one IV infusion.

Administration of EVUSHELD (AZD7442) will comprise 2 sequential IM injections in the gluteal region (1 for each component, cilgavimab [labeled as AZD1061] and tixagevimab [labeled as AZD8895], contained in separate vials), with the second injection administered in the contralateral side.

Immunocompromised participants who received EVUSHELD (AZD7442) at Visit 1 will be offered an optional dose of AZD3152 as an IV infusion at Day 29, after the completion of all Day 29 assessments. Refer to Appendix F for the definition for immunocompromised participants for further guidance on those that qualify for the optional AZD3152 dose.

If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. Similarly, if a participant experiences any AE at any time during IV infusion, the infusion should be stopped. For details on the treatment of anaphylactic reactions after study intervention IM injections and IV infusions, see Appendix E.

AZD3152 IMP will be derived from clonal cell material (from a single production cell line which forms a Master Cell Bank and constitutes the source of the commercial supply).

Each vial of AZD3152, cilgavimab, or tixagevimab contains colorless to slightly yellow, clear to opalescent solutions for infusion or injection. For AZD3152, label-claim volume per vial is 2 mL. For EVUSHELD (AZD7442), label-claim volume per vial is 1.5 mL for each component.

**Table 3 Investigational Products**

| **Intervention name** | **AZD3152** | **EVUSHELD (AZD7442) (cilgavimab [labeled as AZD1061] + tixagevimab [labeled as AZD8895])** |
|---|---|---|
| **Type** | Drug | Drug |
| **Dose formulation** | AZD3152 will be supplied as a single vial.<br>Each AZD3152 vial contains 300 mg solution for infusion or injection. The solution contains 150 mg/mL AZD3152 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 220 mM L-arginine hydrochloride, and 0.04% (w/v) polysorbate 80, at pH 6.0. | EVUSHELD (AZD7442) will be supplied as separate vials of AZD1061 and AZD8895.<br>Each vial contains 150 mg solution for injection. The solutions contain either 100 mg/mL AZD1061 or AZD8895 in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. |
| **Unit dose strength(s)** | 1200 mg AZD3152 at 150 mg/mL | 300 mg EVUSHELD (AZD7442) consisting of 150 mg AZD1061 and 150 mg AZD8895, both at 100 mg/mL |
| **Dosage level(s)** | 1200 mg single dose of AZD3152 | 300 mg single dose of EVUSHELD (AZD7442) (150 mg of AZD1061 and 150 mg of AZD8895) |
| **Vials required** | 4 vials | 2 vials (AZD1061: 1 vial; AZD8895: 1 vial) |
| **Route of administration** | IV infusion at a rate of 50 mg/min (0.33 mL/min) | 2 IM injections (gluteal) of 1.5 mL each [a] |
| **Use** | Investigational | Active-comparator |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | AstraZeneca | AstraZeneca |
| **Packaging and labeling** | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. | IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. |

IM = intramuscular; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; w/v = weight per volume.

[a] The second IM injection will be administered in the contralateral side.

## 6.2 Preparation/Handling/Storage/Accountability

- IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.
- IV line and catheter must be flushed according to local practices to ensure the full dose of AZD3152 is administered. AZD3152 will be administered as an undiluted IV infusion at a rate of 50 mg/minute (0.33 mL/min).
- The Investigator, or an approved designated representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements.
- A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging will be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.
- Study intervention must be kept in original packaging until the time of preparation to prevent prolonged light exposure.
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Detailed dose preparation, labeling for each participant, handling, and administration information will be provided in a separate document such as a Handling Instruction or Pharmacy Manual.

The doses of AZD3152 and EVUSHELD (AZD7442) for administration must be prepared by the pharmacy staff members delegated by the Investigator (or an appropriate designee trained in study drug preparation), using aseptic technique and following local regulations and site requirements. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials (ie, the individual storage time limits are not additive). AZD3152 and EVUSHELD (AZD7442) do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Randomization

Participants will be randomized to receive a single dose of AZD3152 or EVUSHELD (AZD7442) (2:1 ratio). All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be administered at the study visits summarized in the SoA (Table 1).

The IRT/RTSM will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

### 6.3.2 Blinding

Not applicable for this open label sub-study.

### 6.3.3 Procedures for Unblinding

Not applicable for this open label sub-study.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time (if applicable) of dose administered in the clinic will be recorded in the source documents and in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines and over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medication eCRF along with:

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

For healthy participants, EVUSHELD (AZD7442) should not be given within 12 months prior to dosing with study intervention at Visit 1, and 6 months after dosing with any study intervention. SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1. SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. All routine vaccines are permitted; however, they should not be given within 14 days before or after any dose of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks before Visit 1 or during the study until at least after Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. Healthy participants on stable medication can be considered for enrollment based on the judgement of the Investigator.

Table 4 lists the permitted and restricted medications for immunocompromised and immunocompetent participants (excluding healthy participants).

**Table 4 Permitted, Restricted, and Prohibited Medications**

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Permitted | Routine vaccines | All routine vaccines except SARS-CoV-2 vaccines (see the 'Restricted' section below) are permitted; however, they should not be given within 14 days before or after any dose of study intervention. |
| | Allergen immunotherapy | Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study intervention. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants. |
| | Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy) | Allowed. If possible, administration of biologics (eg, adalimumab) should be avoided on the same day as study intervention. |
| | Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting. | |
| Prohibited | None | None |

| Use Category | Type of medication/treatment | Timeline/instructions |
|---|---|---|
| Restricted | Blood/plasma donation | Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after last dose of study intervention; ie, 15 months. |
| | SARS-CoV-2 vaccines | SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1 (see Section 5). SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. |
| | COVID-19 antivirals | COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks prior to Visit 1 or during the study until after the Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed. |
| | Immunoglobulins (IVIG or SCIG) or blood products | Receipt of IV or SC immunoglobulin or blood products within 6 months prior to Visit 1 and expected to receive IV or SC immunoglobulin or blood products 6 months after dosing. |
| | EVUSHELD | EVUSHELD should not be given within 12 months prior to dosing with study intervention at Visit 1, and 6 months after dosing with any study intervention. |

COVID-19 = coronavirus disease 2019; IMP = investigational medicinal product.

## 6.6 Dose Modification

For participants who receive AZD3152 at Visit 1, this is a single dose study. Immunocompromised participants who receive EVUSHELD at Visit 1 will be offered an optional single dose of AZD3152 1200 mg IV at Day 29 after all assessments have been completed. Dose modifications will not be permitted during the study.

## 6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see Section 4.4).

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Dosing for any individual participant will be stopped if a severe or potentially life-threatening serious systemic, allergic, or local reaction occurs during or after receipt of study intervention.

For the IM injections, if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection but before the second IM injection, then the second IM injection should not be given. If this occurs, the participant should remain in the study to be evaluated.

If a participant experiences an AE at any time during IV infusion, the infusion should be stopped, however the participant should remain in the study to be evaluated.

In the opinion of the Investigator or Sponsor, if any significant event should occur, this should be assessed and decided by the Investigator as to whether the participant should proceed in the study or be discontinued.

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

## 7.2 Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed (Table 1).

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for

existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

If any of the stopping criteria detailed in Section 7.2.1 are met, prior approval of a substantial protocol amendment summarizing the emerging data and rationale for restart will be required to support study restart.

### 7.2.1 Stopping Rules

The study will be put on temporary hold (defined as a pause in enrollment of participants into the study) pending further safety data analysis if any SAE or other safety finding is assessed as related to the study intervention that, in the opinion of AstraZeneca warrants suspension of further dosing of participants until the safety finding is fully assessed.

In the event of a temporary hold for safety reasons, AstraZeneca will carefully review the totality of data and the risk to all participants will be evaluated thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing. If AstraZeneca determines that the study may be resumed, this may occur without a protocol amendment.

In addition, the DSMB can recommend temporarily stopping the study or early termination of the study if there is strong evidence that continuation of the study poses a safety concern to participants. In the event of a temporary hold for safety reasons, no additional participants will be randomized or treated with study intervention until review by the DSMB is complete (see Section 9.6).

## 7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

## 7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that, in the opinion of the Sponsor, may preclude further administration of IMP.
- If one or more participant experiences a Grade 4 hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If two or more participants, within the first 45 participants, experience a Grade 3 or higher hypersensitivity reaction.
- If two or more participants, within the first 45 participants, experience a Grade 3 or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with study intervention until the relevant safety review has been conducted.

If the study is suspended, a protocol amendment will be submitted to Health Authorities.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential

and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, and must be captured in the EDC system. This may include results from external laboratories where participants have tested positive for COVID-19.

## 8.1 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

### 8.1.1 Physical Examinations

Full and targeted physical examinations will be performed at the time points as specified in the SoA, and any observations will be documented in the participant's medical records (Table 1).

- A full physical examination will include, but is not limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history in the eCRF.
- A targeted physical examination will include, but is not limited to, areas suggested by the medical history. When there are no new complaints or findings, this should be documented. Each clinically significant abnormal finding following administration of study intervention should be reported as an AE per Section 8.2.

### 8.1.2 Vital Signs

Vital signs, including heart rate, respiratory rate, blood pressure, and body temperature will be performed at the time points as specified in the SoA (Table 1) and collected after the participant has rested in the supine position for at least 5 minutes. For Sentinel Safety Cohort participants on Day 1, vital signs will be monitored predose and again every 15 minutes for up to 2 hours after IMP administration. For all other participants on Day 1, vital signs will be performed predose and again 10 to 15 minutes after IMP administration.

Situations in which vital sign results should be reported as AEs are described in Section 8.2.7.

### 8.1.3 Electrocardiograms

A single 12-lead ECG will be performed at screening (time points specified in the SoA; see Table 1). A 12-lead ECG will be obtained after 5 minutes' supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal, borderline, or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as unscheduled assessments.

All ECG readings will be digitally stored as source documents.

### 8.1.4 Clinical Safety Laboratory Assessments

The serum chemistry, hematology, and coagulation analyses will be performed at a local laboratory at or near to the study site for all participants (see Table 1).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables that will be measured are listed in Table 5.

**Table 5 Laboratory Safety Variables**

| **Hematology** | |
|---|---|
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |

**Table 5 Laboratory Safety Variables**

| | |
|---|---|
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea (or blood urea nitrogen) | Aspartate aminotransferase (AST) |
| Creatinine (and estimated glomerular filtration rate [eGFR]) | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total bilirubin (TBL) |
| Calcium | Conjugated bilirubin |
| Phosphate | Troponin T or I (screening only) |
| Glucose (random) | |
| **Coagulation** | |
| Activated partial thromboplastin time (aPTT) | Prothrombin time (PT) (or international normalized ratio) |
| **Other (women of childbearing potential only)** | |
| Urine or serum (β-hCG) pregnancy test | Follicle stimulating hormone [a] |

[a] For female participants aged < 50 years who are considered postmenopausal, will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D for further instructions.

β-hCG = beta human chorionic gonadotropin; ULN = upper limit of normal.

For female participants aged < 50 years who are considered postmenopausal, an FSH evaluation will be performed at screening if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment.

For WOCBP only, a urine or serum β-hCG pregnancy test will be performed at screening, Visit 1, and Day 29 for those participants who receive AZD3152 at that visit. Urine or serum pregnancy test must be performed and be negative prior to dosing at each dosing visit.

## 8.1.5 Other Safety Assessments

### 8.1.5.1 Immediate Adverse Events

Participants will be kept under observation for 2 hours (Sentinel Safety Cohort) or 1 hour (Full Sub-study Cohort) after study intervention administration to ensure their safety. Any AE that occurs during this period will be noted on the source document and in the eCRF.

As with any biologic product, hypersensitivity reactions (including anaphylaxis) and injection site reactions are possible. Therefore, appropriate drugs and medical equipment to treat these

reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Management of anaphylaxis and hypersensitivity should be performed in accordance with current standard of care and clinical guidelines.

Any AEs should be reported as described in Section 8.2.

#### 8.1.5.2 Injection Site Reaction (IM administrations) and Infusion-related Reactions (IV administration)

Injection site reactions and infusion-related reactions may be observed and may manifest as local inflammation, redness, itching, pain, swelling, bruising, and possible bleeding or infection at the site of injection/infusion. Diameters of any redness/swelling may be recorded in the medical record at site visits.

Injection site reactions and infusion-related reactions will be monitored on the day of dosing (Table 1). The injection site reactions and infusion-related monitoring will be performed immediately after, 30 minutes (+ 10 minutes), 2 hours after dosing is complete on Day 1 (Sentinel Safety Cohort), or 1 hour after the study intervention (injection/infusion) is/are complete (Full Sub-study Cohort), and prior to participant release. Injection site reactions and infusion-related reactions will also be monitored at the Day 8 visit. For immunocompromised participants who received EVUSHELD as their first dose and accept the offer of a second dose with AZD3152, infusion-related reactions will also be monitored at Day 36.

Any AEs should be reported as described in Section 8.2.

## 8.2 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or equivalent representative as locally defined).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.2.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of study intervention administration through 29 days following administration of study intervention. However, if AEs occur outside of this window that are either related to IMP, COVID-19, or asymptomatic SARS-CoV-2 infection, these should also be reported on the AE CRF page. Serious adverse events, MAAEs, and

AESIs will be collected throughout the study.

Any AESIs will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention (see Section 8.2.4).

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

### 8.2.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- If the AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

Severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017), and are described in Appendix B.

### 8.2.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medications and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

### 8.2.4 Adverse Events of Special Interest

Adverse events of special interest will be programmatically identified through AE information that is collected in the eCRF and will be assessed from the time of study intervention.

An AESI is an event of scientific and medical interest, specific to the further understanding of the safety profile of the study intervention, and requires close monitoring and rapid communication by the Investigators to AstraZeneca. An AESI can be serious or non-serious.

The AESIs for AZD3152 and EVUSHELD in this study are based on those identified for EVUSHELD and are as follows:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Infusion-related reactions (for IV administration)
- Cardiovascular and thrombotic events

### 8.2.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoA (Table 1).

Medically attended adverse events are defined as AEs leading to medically-attended visits that

were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit will not be considered MAAEs.

### 8.2.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE.

### 8.2.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

### 8.2.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs.

Where AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN occurs, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.2.9 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference documents for definition of expectedness/listedness for AZD3152 and the active comparator product EVUSHELD are the respective Investigator's Brochures for the individual products.

## 8.2.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

### 8.2.10.1 Maternal Exposure

The IMP should not be given to pregnant women.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.2.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

## 8.2.11 Medication Error, Drug Abuse, and Drug Misuse

### 8.2.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.2.9) and **within 30 days** for all other medication errors.

#### 8.2.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication errors can be found in Appendix B 4.

#### 8.2.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

#### 8.2.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

## 8.3 Overdose

For this study, any dose of study intervention (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 3).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or**

**5 calendar days** for overdoses associated with an SAE (see section 8.2.9) and **within 30 days** for all other overdoses.

## 8.4 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.4.1 Pharmacokinetics

Serum concentrations will be used to estimate predicted SARS-CoV-2 nAbs, the primary analysis (see Section 9.4.2). Additionally, characterization of the PK of AZD3152 and AZD7442 (EVUSHELD) in serum is a secondary objective of this study. Samples will be collected for measurement of concentrations of these analytes as specified in the SoA (Table 1).

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons.

Serum concentrations will be used to estimate predicted SARS-CoV-2 nAbs over time for each mAb individually, and where applicable, for each combination.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.4.1.1 Determination of Drug Concentration

Samples for determination of concentrations of AZD3152 and AZD7442 (EVUSHELD), in

total and for each component mAb in AZD7442 (EVUSHELD), in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using appropriately validated and qualified bioanalytical methods. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

### 8.4.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments in serum will be collected according to the SoA (Table 1). Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.4.2.1 Anti-drug Antibody Assessments

Blood samples for determination of ADA to AZD3152 and AZD7442 (EVUSHELD) in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate Bioanalytical Report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination, and may also undergo further anti-drug nAbs characterization.

ADA response to AZD3152 and AZD7442 (EVUSHELD) will not be included in the primary analysis and will be reported in the final CSR.

#### 8.4.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess prior exposure to SARS-CoV-2, using qualitative nucleocapsid serology assay.

#### 8.4.2.3 SARS-CoV-2 Neutralizing Responses

Serum samples to measure SARS-CoV-2 nAb levels will be collected according to the time points specified in the SoA (Table 1). Authorized laboratories will measure SARS-CoV-2 nAbs using a pseudovirus neutralization assay.

Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory

Manual.

#### 8.4.2.4 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Exploratory serum samples may be utilized to investigate additional humoral immune responses, as determined by the Sponsor based upon emerging safety, efficacy, immunobridging, and immunogenicity data.

## 8.5 Human Biological Sample Biomarkers

Human biological samples for biomarkers analysis will not be collected in this study.

## 8.6 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

## 8.7 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Participants' data will be presented by the dosing regimen received.

The planned analyses (and reporting) of the sub-study results will be conducted independently from the SUPERNOVA Parent study.

## 9.1 Statistical Hypotheses

A noninferiority comparison will be performed using the ratio of predicted SARS-CoV-2 nAb GMTs (GMTR) at Visit 3 (Day 29) of the XBB.1.5 variant (or other circulating VOC) for participants receiving AZD3152 versus the alpha variant for participants receiving EVUSHELD with a comparability threshold of 0.8, ie, non-inferiority will be concluded if the 2-sided 90% CI for the GMTR is > 0.8. Demonstration of non-inferiority provides 95% confidence participants treated with AZD3152 will have nAb titers associated with protection for symptomatic COVID-19 observed in PROVENT.

If the null hypothesis is rejected in favor of the alternative, the data provide evidence that the predicted GMTs of XBB.1.5 variant (or other circulating VOC) nAbs in participants receiving AZD3152 are not inferior to predicted Alpha variant nAb GMTs in participants receiving EVUSHELD within the comparability threshold.

Null hypothesis: predicted GMT ratio $\leq 0.80$

Alternative hypothesis: predicted GMT ratio $> 0.80$

If non-inferiority is established, then superiority will be assessed and concluded if the 2-sided 95% CI excludes one. A positive result of the superiority test would provide further assurance of the nAb comparability.

## 9.2 Sample Size Determination

Approximately 450 participants will be randomized in a 2:1 ratio to receive AZD3152 or EVUSHELD. The sample size was chosen to support bridging to EVUSHELD through assessment of the primary objective with a noninferiority comparison of the predicted serum GMTs of Day 29 nAbs against the SARS-CoV-2 XBB.1.5 variant (or other circulating VOC) for AZD3152 vs Alpha variant for EVUSHELD. A sample size of 300 participants on AZD3152 and 150 on EVUSHELD provides > 90% power to declare noninferiority using a lower comparability threshold of 0.8 assuming a true GMTR of 1.0, a common gSD of 2.0, a 1-sided Type I error rate of 5%, a 5% attrition rate, and > 95% power to evaluate superiority with an assumed GMTR of 2.0.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 6 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Full analysis set (FAS)/ Safety analysis set | All randomized participants who received part or all of study intervention. Participants will be classified according to the assigned treatment they are randomized to. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.<br><br>The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment. |
| Pharmacokinetics analysis set | All participants in the FAS with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment.<br>Participants with protocol deviations that may interfere with the serum concentrations or interpretation of PK parameters may be excluded or have data collected after the protocol deviations set to missing. |

mAb = monoclonal antibody; PK = pharmacokinetics.

## 9.4 Statistical Analyses

The SAP will be finalized prior to the primary database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints

including primary and secondary endpoints to be evaluated.

### 9.4.1 General Considerations

This sub-study is designed to evaluate the safety, PK, and neutralizing activity of AZD3152 compared with EVUSHELD for pre-exposure prophylaxis of COVID-19. The primary endpoint is safety as well as non-inferiority of the predicted SARS-CoV-2 nAb GMTs for the XBB.1.5 variant (or other circulating VOC) (following AZD3152 administration) and Alpha variant (following EVUSHELD administration). To align with the PK analysis set, all treatment groups will be presented by the treatment actually received unless otherwise specified.

Safety data from the sub-study will also be used to support the evaluation of AZD3152 for treatment.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received. Methods for controlling multiplicity across endpoints will be presented separately in the SAP for the bridging analysis.

### 9.4.2 Primary Analysis – Predicted SARS-CoV-2 nAb Response

The primary analysis will evaluate the log-transformed, predicted Day 29 SARS-CoV-2 nAb titers as the primary outcome variable for the Alpha variant and XBB.1.5 variant (or other circulating VOC). Serum PK (ng/mL) from the EVUSHELD arm will be divided by the Alpha $IC_{50}$ value of 2.1 (ng/mL) and the AZD3152 arm by the XBB.1.5 $IC_{50}$ of 5.8 ng/mL (or the $IC_{50}$ of the other circulating VOC) to derive the predicted Day 29 nAb titers for each variant. The $IC_{50}$ values used for this analysis were determined by Monogram Biosciences (South San Francisco, CA) using the pseudovirus neutralization assay. Additional analysis may explore alternative in-vitro $IC_{50}$ values and quantify differences in the predicted and observed SARS-CoV-2 nAb levels at Day 29. Details will be specified in the SAP on each analysis.

The statistical methodology for the primary analysis will be based on a 2-sided 90% CI of the ratio of the predicted GMTs to compare across variants. See Section 9.1 for details regarding the hypothesis testing for the primary endpoint of noninferiority in the predicted GMT ratio of XBB.1.5 to Alpha variant nAbs. The 2-sided 90% CI for the ratio of predicted GMTs will be calculated using normal approximation of log-transformed concentrations.

### 9.4.3 Characterization of Predicted SARS-CoV-2 nAb Titers with Measured nAb Titers

To characterize the correlation between predicted SARS-CoV-2 nAbs and the change from baseline in measured serum SARS-CoV-2 nAbs against the relevant SARS-CoV-2 variant for AZD3152, both predicted and measured SARS-CoV-2 nAb titers as well as the change from baseline in measured titers will be summarized by treatment arm. Correlation between predicted and measured titers will be estimated within each treatment arm.

### 9.4.4 SARS-CoV-2 Neutralizing Antibody Responses

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (see Section 1.3). Samples collected from participants will be evaluated for the Alpha variant and XBB.1.5 variant (or other circulating VOC), and may also be evaluated for additional variants, using validated pseudovirus neutralization assays.

### 9.4.5 Anti-drug Antibody Variables

The ADA variables will be assessed and summarized by number and percentage of participants by treatment group based on the respective ADA analysis set for each mAb or combination of mAbs. The ADA titer will be listed by participant at different time points. The potential impact of ADA on safety (association with AEs and SAEs) and PK will be assessed. Further details are provided in the SAP.

### 9.4.6 Safety

Adverse events and SAEs will be coded using the most recent version of MedDRA, where possible, and will be summarized by SOC and preferred term and by intensity and relationship to study intervention as judged by the Investigator. All parameters for laboratory assessments, vital signs, and physical examination will be summarized with descriptive statistics based on data type (continuous, categorical, etc).

### 9.4.7 Pharmacokinetics

Following initial dosing with AZD3152 or EVUSHELD, individual mAb serum concentrations will be summarized using descriptive statistics by treatment group over time.

## 9.5 Planned Analyses

Two planned analyses will be conducted. The primary analysis will take place after all study participants complete Visit 3 (Day 29) or have withdrawn from the study. The final analysis will take place after the end-of-study visit. The Day 29 primary analysis will present available safety, PK, and predicted SARS-CoV-2 nAb data to evaluate the primary objectives of the study. The final analysis will include all available data collected through the follow-up period of 15 months from Day 1. Additional interim analyses may be conducted to support regulatory

requirements or at the discretion of the Sponsor.

If there is a medical need for AZD3152 to be submitted for health authority review urgently, additional analysis may need to be conducted. The SAP and Statistical Integrity Plan will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

## 9.6 Data Safety Monitoring Board

An independent DSMB will provide oversight to ensure the safe and ethical conduct of the study.

The DSMB will meet periodically, review safety data in an unblinded manner, and make any necessary recommendations to AstraZeneca based on its evaluation of emerging data, with ad hoc meetings being scheduled, if needed. These reviews will be based on preliminary data that will not have been subject to validation and database lock.

If required, the DSMB will recommend temporarily stopping or termination of the study.

The following safety parameters will be assessed as part of the DSMB review:

- AEs (including immediate AEs and injection site reactions)
- AESIs
- SAEs
- MAAEs
- Safety laboratory parameters

The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix A Regulatory, Ethical, and Study Oversight Considerations

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

Applicable ICH GCP Guidelines

Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for Suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about such breaches.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the Regulatory Authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

- The Investigator should have a process in place to ensure that:

The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach

A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

## A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

## A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform an ongoing combination of source data review and source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

## A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Monitoring Plan.

## A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but

are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the DSMB, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

# Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

## B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

**Life-threatening**

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

**Hospitalization**

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**Important Medical Event or Medical Treatment**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**Severity Rating Scale:**

The following severity ratings will be used, adapted from the CTCAE v5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.

- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

## B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression

'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

# B 4 Medication Error, Drug Abuse, and Drug Misuse

### 10.1.1 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

### 10.1.2 Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

### 10.1.3 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

# Appendix C Handling of Human Biological Samples

## C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

## C 3 International Airline Transportation Association 6.2 Guidance Document

**LABELING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
**Category A Pathogens** are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

# Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

## D 2 Definitions

**Potential Hy's Law**: AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase.

**Hy's Law**: AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

# D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Local Laboratories Being Used:**

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:

Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.

Complete the three Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

**Where there is an agreed alternative explanation** for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

## D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

**Hy's Law Laboratory Kit for Central Laboratories**

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV |

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| | HBsAg<br>IgM and IgG anti-HBc<br><br>HBV DNA [a]<br>IgG anti-HCV<br>HCV RNA [b]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM and IgG anti-CMV<br>IgM and IgG anti-HSV<br>IgM and IgG anti-EBV |
| Alcoholic hepatitis | CD-transferrin |
| Autoimmune hepatitis | ANA<br>Anti-LKM Ab<br>ASMA |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin<br>Transferrin saturation |

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
Ab = antibody; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein–Barr virus; GGT = gamma glutamyl transpeptidase; HAV = hepatitis A virus; HBc = hepatitis B core antibody; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; LKM = liver/kidney microsomal.

# Appendix E Anaphylaxis

The National Institute of Allergy and Infectious Disease (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) clinical criteria for diagnosing anaphylaxis are as follows (Sampson et al 2006):

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled**

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
   (a) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   (a) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure
   (b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Low systolic blood pressure for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 × age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.

To assist with the mitigation of these AEs, see Table E1, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of study intervention. Final treatment is at the discretion of the Investigator and

should reflect local standard of care.

**Table E1 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Mild local reactions (During and post injection and hypersensitivity)**<br>Mild injection site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement. | Evaluate participant, including close monitoring of vital signs.<br>At the discretion of the Investigator, treat participant, for example, with:<br>Localized cold pack or heat to the injection site.<br>If more generalized reaction:<br>• Diphenhydramine 50 mg PO or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Topical antihistamines and/or low-potency topical corticosteroid preparations and/or<br>• Anti-nausea medication, as needed. | Pause or hold additional study intervention injection immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |
| **Moderate reactions (during or immediately post injection)**<br>Injection site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below). | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• Anti-nausea and/or antiemetic intramuscular, as needed. | Stop or hold additional study intervention administration immediately.<br>At the discretion of the Investigator, resume current study intervention administration under observation. |

**Table E1 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Moderate hypersensitivity reactions**<br>Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mm Hg change in systolic BP from pre-infusion measurement. | Evaluate participant, including close monitoring of vital signs.<br>Treat participant, for example, with:<br>• Normal saline (~500 to 1000 mL/hour IV) and/or<br>• Diphenhydramine 50 mg IV or equivalent and/or<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg. | Stop study intervention administration immediately. |

**Table E1 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions**

| Severity of Symptoms | Treatment | Study Intervention |
|---|---|---|
| **Severe**<br>Above plus fever with rigors, hypo- or hypertension with ≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope,<br>incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor<br>OR<br>**Life-threatening**<br>Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion. | Evaluate participant, including close monitoring of vital signs.<br>Maintain airway, oxygen if available.<br>Treat participant immediately, for example with:<br>• Normal saline (~500 to 1000 mL/hour IV)<br>• Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local SOC, example, epinephrine 1:1000, 0.5 to 1.0 mL administered SC for mild cases and intramuscular for more severe cases<br>• IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg<br>• Diphenhydramine 50 mg IV or equivalent<br>• Acetaminophen 500 to 650 mg or equivalent dose of paracetamol<br>Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator.<br>Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine<br>Grade 4 event<br>At the discretion of the Investigator | Stop study intervention administration immediately. Do not resume current dosing. Permanently discontinue study intervention administration.<br>Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days. |

BP = blood pressure; IV = intravenous; PO = per os (oral); SC = subcutaneously; SOC = standard of care.

# Appendix F Definitions for Healthy and Immunocompromised Participants

Participants are defined as healthy if they satisfy all of the following criteria:

- Have no active infection with hepatitis B or C
- Have serum creatinine, AST, or ALT ≤ 1.5 × ULN at screening
- Have no history of malignancy other than treated non-melanoma skin cancers or locally-treated cervical cancer in previous 5 years
- Have additional safety laboratory test values within normal range at screening
- SARS-CoV-2 vaccines should not be given within 3 months prior to Visit 1. SARS-CoV-2 vaccines should also not be given during the study until after the Day 29 assessments. All routine vaccines are permitted; however, they should not be given within 14 days before or after any dose of study intervention. COVID-19 antivirals for prophylaxis should not be given within at least 2 weeks before Visit 1 or during the study until at least after Day 29 assessments. If the participant develops COVID-19, standard of care treatment is allowed.
- Healthy participants on stable medication can be considered for enrollment based on the judgement of the Investigator.

Participants are defined as immunocompromised if they satisfy at least 1 of the following risk factors at enrollment:

- Have solid tumor cancer and be on active immunosuppressive treatment
- Have hematologic malignancy
- Transplant participants must satisfy at least one of the following:
  - Have had a solid organ transplant within 2 years and /or
  - Had a hematopoietic stem cell transplant within 2 years and / or
  - Who have chronic graft-versus-host disease
  - Participants who previously had a solid organ transplant or hematopoietic stem cell transplant may also be eligible based on the inclusion criterion for immunosuppressive treatment
- Are actively taking immunosuppressive medicines (eg, are using corticosteroids [ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive [eg, Bruton's tyrosine kinase inhibitors], tumor-necrosis blockers, or other immunosuppressive biologic agents (eg, for rheumatic diseases)
- Received chimeric antigen receptor T-cell therapy

- Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Have a moderate or severe primary (eg, DiGeorge syndrome) or secondary (eg, hemodialysis) immunodeficiency

See Table F1 for the list of qualifying immunosuppressive medications.

**Table F1 List of Immunosuppressive Medications**

The list of immunosuppressive medications in the table below is not exhaustive.

| **1. Alkylating Agents** | |
|---|---|
| Bendamustine | Melphalan |
| Busulfan | Mitomycin |
| Carboplatin | Oxaliplatin |
| Carmustine | Procarbazine |
| Cisplatin | Streptozocin |
| Cyclophosphamide | Temozolomide |
| Dacarbazine | Thiotepa |
| Ifosfamide | Trabectedin |
| Lomustine | |

| **2. Selective Immunosuppressants** | | | | | |
|---|---|---|---|---|---|
| General | | Calcineurin Inhibitors | Antimetabolites | | |
| Azathioprine | Lenalidomide | Cyclosporine | Methotrexate | Clofarabinr | |
| Belumosudil | Mycophenolate | Tacrolimus | Nelarabine | Cytarabine | |
| Bortezomib | Pomalidomide | Voclosporin | Pemetrexed | Decitabine | |
| Cladribine | Terifflunomide | | Pralatrexate | Floxuridine | |
| Dimethyl Fumarate | Thalidomide | | Irinotecan | Fludarabine | |
| Diroximal Fumarate | Anti-thymocyte immunoglobulin (horse, rabbit) | | Liposome | Fluorouracil | |
| Leflunomide | | | Capecitabine | Gemcitabine | |
| | | | | Mercaptopurine | |

| JAK Inhibitors | mTOR Inhibitors | Sphingosine-1-phosphate Receptor Modulators |
|---|---|---|
| Baricitinib<br>Tofacitinib<br>Upadacitinib<br>Peficitinib<br>Itacitinib | Everolimus<br>Sirolimus | Fingolimod<br>Ozanimod<br>Ponesimod<br>Siponimod |
| **3. Monoclonal Antibodies** | | |
| General | Anti-IFN | Anti-CD20 |
| Alemtuzumab (anti-CD52)<br>Belimumab<br>Begelomab (anti DPP-4/CD26)<br>Teprotumumab (anti-IGF-1)<br>Inebilizumab (anti-CD19)<br>Muromonab (anti-CD3)<br>Inotuzumab Ozogamicin (anti-CD22) | Anifrolumab<br>Emapalumab | Ibritumomab<br>Obinutuzumab<br>Rituximab<br>Ocrelizumab<br>Ofatumumab |
| Selective T-Cell Costimulation Blockers | Integrin Receptor Agonists | Bruton Tyrosine Kinase Inhibitors |
| Abatacept<br>Belatacept | Natalizumab<br>Vedolizumab | Ibrutinib<br>Acalabrutinib<br>Pirtobrutinib<br>Zanubrutinib<br>Deucravacitinib |
| Complement Inhibitors | TNF-alpha Inhibitors | IL-23 Inhibitors |
| Pegcetacoplan<br>Eculizumab (anti-C5)<br>Ravulizumab (anti-C5)<br>Sutimlimab (anti-C1) | Adalimumab<br>Afelimomab<br>Certolizumab Pegol<br>Etanercept<br>Golimumab<br>Infliximab | Ustekinumab<br>Guselkumab<br>Tildrakizumab<br>Risankizumab |

| IL-17 Inhibitors | IL-1 Inhibitors | IL Inhibitors (other) |
|---|---|---|
| Secukinumab<br>Ixekizumab<br>Bimekizumab<br>Brodalumab<br>Netakimab | Anakinra<br>Canakinumab<br>Rilonacept | Basilximab (anti IL-2)<br>Sarilumab (anti IL-6)<br>Satralizumab (anti IL-6)<br>Siltuximab (anti IL-6)<br>Tocilizumab (anti IL-6)<br>Spesolimab (anti IL-36) |
| **4. Steroids** | | |
| Dexamethasone: ≥ 3 mg per day, minimum of 2 weeks of therapy<br>Prednisolone: ≥ 20 mg per day, minimum of 2 weeks of therapy<br>Prednisone: ≥ 20 mg per day, minimum of 2 weeks of therapy | | |

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