Clinical Study Protocol	
Study Intervention	AZD3152
Study Code	AZ-RU-00002
Version	3.0
Date	02 Aug 2023

A Phase II Randomized, Double-blind Study to Evaluate the Safety, Neutralizing Activity and Efficacy of AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants having an Increased Risk for Inadequate Response to Active Immunization (NOVELLA)

Sponsor Name: AstraZeneca Pharmaceuticals LLC

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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: AZ-RU-00002

Amendment Number: 3.0

Study Intervention: AZD3152, a novel monoclonal antibody (mAb) against SARS-CoV-2 or placebo [redacted]

Study Phase: II

Title: A Phase II Randomized, Double-blind Study to Evaluate the Safety, Neutralizing Activity and Efficacy of AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants having an Increased Risk for Inadequate Response to Active Immunization

Acronym: NOVELLA

Study Physician / Coordinating Investigator / Principal Investigators Name and Contact Information will be provided separately

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 3.0	17-Jul-2023
CSP Version 2.0	14-Jun-2023

Overall Rationale for the Modification:

The protocol has been amended primarily to change the comparator from (active) AZD7442 (EVUSHELD) to placebo. This change was initiated to bring the design of the local study in line with the recent changes in the Main Cohort of ongoing Phase I/III global study (SUPERNOVA, NCT05648110). Comparative evaluation with placebo is the most informative and appropriate option at the current stage of clinical development program.

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	The comparator has been changed from (active) AZD7442 (EVUSHELD) to placebo. As placebo comparator will be given as a single injection (whereas AZD7442 previously required two injections) at each dosing occasion, the injection of matching placebo that was part of the blinded AZD3152 administration has been removed	Bringing the design of the local study in line with the recent changes in the Main Cohort of ongoing Phase I/III global study (SUPERNOVA, CCI [redacted])
1.1 Synopsis 4.1 Overall Design 4.3.2 Justification for Placebo	Added justification for use of placebo as a comparator	Justification required due to the change of comparator

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Global change	The coding name "AZD7442" has been changed to current trade name "EVUSHELD" throughout the document	Clarification of the text
Schedule of Activities	Remove of Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection) assessment on Day 1	Clarification
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 urine 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
2.2.1 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
4.3 Justification for Dose	Removed sub-section "Justification for AZD7442 Dose"	Comparator is now placebo
6.5 Concomitant Therapy	In the table, the timeline for COVID-19 antivirals and EVUSHELD 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	Timeframe updated for consistency with AE collection period noted in Section 8.3.1

Section Number and Name	Description of Change	Brief Rationale
	randomization) should be reported as an AE	
9.4.3 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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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase II Randomized, Double-blind Study to Evaluate the Safety, Neutralizing Activity and Efficacy of AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants having an Increased Risk for Inadequate Response to Active Immunization

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.

This Phase II study will assess the safety and neutralizing activity of AZD3152 in adults with conditions increasing risk of inadequate protective immune response after vaccination and thus are at high risk of developing severe COVID-19.

Evaluation of safety and efficacy compared to placebo is a generally accepted approach in the early stages of clinical development of monoclonal antibodies (Decision of Council of the Eurasian Economic Commission November 3, 2016 №89 «Rules for conducting research on biological medicines in the Eurasian Economic Union»). This approach provides optimal comparative data for subsequent interpretation, is ethically justified and does not carry any additional risks in the conditions of a favourable change in the epidemic situation in the Russian Federation (in 2022, Rospotrebnadzor lifted restrictions imposed in connection with the pandemic). In addition, uneven inclusion in the study groups is planned – fewer participants will receive a placebo. All participants will be able to receive SARS-CoV-2 vaccines after the Day 29 assessments.The results of this study will provide clinical data on safety, neutralizing activity and efficacy of an innovation drug in the new region (the Russian Federation), which will be a mandated by Russian law additional data source for the AZD3152 marketing authorization in Russia and will help expand the available range of COVID-19 prophylaxis strategy in conditions of continually virus evolving.

Objectives and Endpoints

Objectives	Estimand Descriptions/Endpoints
Primary	
To evaluate the safety of AZD3152 compared with placebo	**Population:** Safety analysis set **Endpoints:** • Occurrence of AEs collected throughout the study • Occurrence of SAEs, MAAEs, and AESIs collected throughout the study **Intercurrent events:** Treatment policy will be applied, i.e., all events collected will be included in the

	analysis regardless of the presence and timing of intercurrent events. **Summary measure:** The number and proportion of subjects with AEs, SAEs, MAAEs, AESIs.
Secondary	
To compare the nAb responses to the SARS-CoV-2 emerging dominant variant(s) of concern circulating during the course of the study in serum following AZD3152 or placebo administration	**Population:** SARS-CoV-2 nAb analysis set **Endpoint:** Titer for SARS-CoV-2 emerging dominant variant(s) nAbs **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 this endpoint (i.e., while-on-treatment strategy is applied). **Summary measure:** Geometric mean titer (GMT) and geometric mean fold rise (GMFRs) (from baseline value through Day 29 after the single IM dose) of SARS-CoV-2 nAbs. Descriptive statistics for the log-transformed titer will include the number of participants, GMT and GMFR, corresponding gSD, 95% CI, minimum, and maximum and summarized by treatment arm.
To compare the incidence of symptomatic COVID-19 cases in participants receiving study intervention. (efficacy)	**Population:** Full analysis set **Endpoint:** Incidence of a post-treatment symptomatic COVID-19 case (negative RT-PCR at baseline to positive RT-PCR or positive antigen test at any time up to 6 months AND symptoms specified in the modified WHO definition of symptomatic COVID-19). **Intercurrent events:** 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 have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied). **Summary measure:** incidence of a post-treatment symptomatic COVID-19 case.
Exploratory	
CCI [redacted]	**Population:** CCI [redacted]

CCI	**Endpoints:** CCI CCI CCI
CCI	**Population:** CCI **Endpoint:** CCI **Intercurrent events:** CCI **Summary measure:** CCI

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization

Overall Design

This is a Phase II study that will be conducted in approximately 116 participants to evaluate the safety, neutralizing activity and efficacy of AZD3152.

Participants will be randomized in a 3:1 ratio to receive AZD3152 (300 mg, 2 mL) or placebo (2 mL) administered IM in the anterolateral thigh.

Study intervention will be handled by an unblinded pharmacist (or designee, in accordance with institutional regulations) at the study site who will be independent of safety evaluations and other trial evaluations.

If, following study intervention administration, a subject develops COVID-19, according to the Provisional recommendations on the methods for prevention, diagnosis and treatment of novel coronavirus infection (COVID-19), issued by the Ministry of Health of the Russian Federation, version 17 dated December 14, 2022 (Provisional recommendations 2022) (s)he must call "122" to be visited by a healthcare professional who, among other procedures, will perform a COVID-19 test. Once a visit by a healthcare professional has been requested, the subject must notify the study doctor of the date symptoms occurred and the date a healthcare professional visit has been requested, as soon as possible. Also, once a test result is available, the participant must report within 3 days the date of test and its result to the Investigator. If the test result is positive, the Investigator (or his/her delegate, according to the local regulations and institution guidelines) will make telephone calls ***every three days*** to collect safety data until the subject informs about his/her recovery.

Disclosure Statement:

This is a parallel group, safety, neutralizing activity and efficacy evaluation study.

Number of Participants:

In total, approximately 87 participants will be exposed to a single dose of AZD3152 (300 mg, 2 mL) IM, and 29 participants will be exposed to a single dose of placebo (2 mL) IM.

Intervention Groups and Duration:

Single dose of AZD3152 (300 mg, 2 mL) IM or placebo (2 mL) IM.

The duration of each participant's involvement in the study will be approximately 6 months from when the study intervention is administered.

Statistical Methods

Categorical variables will be presented as frequencies and proportions in percent values. Continuous variables will be presented as means, geometric means (where applicable), standard deviations, geometric standard deviations (where applicable), medians, minimum and maximum, and quartiles (where applicable), with number of observations. CCI [redacted] All

the variables will be descriptively compared between treatment arms.

An interim analysis is planned after 116 participants have completed visit 4 (Day 29) to evaluate early safety and efficacy data at Day 29.

This interim analysis will include primary endpoint variables: all AEs, SAEs, MAAEs, and AESIs and secondary efficacy endpoints: nAb responses to the SARS-CoV-2 emerging dominant variant(s) and incidence of symptomatic COVID-19 cases (only if at least one case will be reported at time of data cut-off). This interim analysis will be provided by unblinded team. All the parameters, along with other results (disposition, demographic data etc.) will be provided by treatment arms. The comparisons between treatment arms will be performed descriptively.

The final analysis will be performed once all participants complete Visit 6 (Day 181) or early withdrawal from the study.

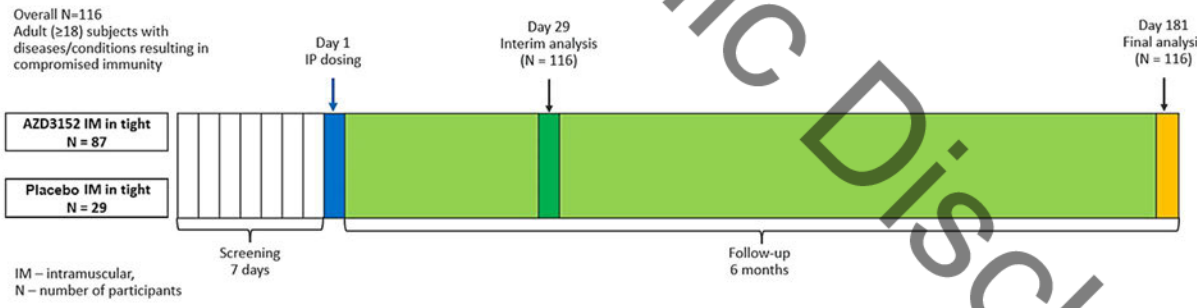
CCI [redacted]

Interim and final analyses will be described in detail in the Statistical Analysis Plan.

1.2 Schema

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

Figure 1 Study Design



Note: An interim analysis is planned after 116 participants have completed Visit 4 (Day 29). A final analysis will occur after all participants have completed Visit 6 (Day 181) or have withdrawn from the study. The study will maintain a double-blinded (i. e., blind for participants, Investigators/site staff, and AstraZeneca) until the primary analysis

1.3 Schedule of Activities

The study will consist of 2 periods: a screening period of up to 7 days (Day -7 through Day -1), and a treatment and follow-up period lasting 6 months after the administration of study

intervention (Table 1).

For participants with qualifying symptoms of COVID-19, additional telephone contacts performed every 3 days should be incorporated in the schedule.

1.3.1 Screening, Treatment and Follow-up Activities

Table 1 Schedule of Activities

Procedure	Screening	Treatment and Follow-up Period						
Visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**EDV**
Day	**-7 to -1**	**1**	**8**	**15**	**29**	**91**	**181**	**NA**
Window (days)	**NA**	**NA**	**± 3**	**± 3**	**+ 3**	**± 5**	**± 14**	**NA**
Written informed consent	X							
Verify eligibility criteria	X	X (predose)						
Randomization		X (predose)						
Medical history and demographics (including COVID-19 vaccine status and previous COVID-19 infection)	X							
Full physical examination, including height and weight	X							X
Targeted physical examination based on medical history		X (predose)						
Vital signs	X	X[a]	X				X	X
Serum chemistry, hematology, coagulation (local laboratory)	X		X		X			X
Troponin, high-sensitivity test (local laboratory)	X[b]							

Procedure	Screening	Treatment and Follow-up Period						
Visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**EDV**
Day	**-7 to -1**	**1**	**8**	**15**	**29**	**91**	**181**	**NA**
Window (days)	**NA**	**NA**	**± 3**	**± 3**	**+ 3**	**± 5**	**± 14**	**NA**
Follicle stimulating hormone[c]	X							
HIV test	X							
Electrocardiogram (single, to be performed locally if feasible) [d]	X							
Urine pregnancy test or serum β-hCG (WOCBP only)	X	X[e]						
Rapid antigen test for SARS-CoV-2 (performed locally)		X [f]						
Weekly telephone/email/text contacts-monitoring for safety and COVID-19 qualifying symptom		←——————X——————→						
Assessment of AEs		X						X
Assessment of SAEs, MAAEs, and AESIs	X (SAEs)	X (ongoing observation and questioning)						X
Concomitant medications	X	X (ongoing observation and questioning)						X
CCI [redacted]		X (predose)			X	X	X	X

Procedure	Screening	Treatment and Follow-up Period						
Visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**EDV**
Day	**-7 to -1**	**1**	**8**	**15**	**29**	**91**	**181**	**NA**
Window (days)	**NA**	**NA**	**± 3**	**± 3**	**+ 3**	**± 5**	**± 14**	**NA**
SARS-CoV-2 nAb serum sample[h]		X (predose)	X	X	X	X	X	X
CCI [redacted]		X (predose)			X	X	X	X
Study intervention administration		X						
Injection site reaction monitoring		X[j]	X					
Immediate AEs[k]		X						

[a] On dosing day, vital signs will be performed predose and again approximately 10 to 15 minutes after injection. Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.
[b] It is acceptable for this to be performed on Day 1 (predose). Test results must be available prior to dosing.
[c] If applicable, for female participants aged < 50 years and have been amenorrhoeic for 12 months and considered postmenopausal follicle stimulating hormone test should be done before dosing.
[d] 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.
[e] Sample urine or serum β-hCG pregnancy test must return a negative result before dosing.
[f] Sites will be provided with rapid antigen tests to be done in participants at sites before study intervention administration at Visit 1.
[h] In each timepoint should be collected 2 aliquots each 3 mL (A and B), according to Investigational product handling manual.
[i] CCI [redacted].
[j] Perform immediately, 30 minutes (+ 10 minutes) and 1 hour after injection, and prior to participant release.
[k] Immediate AEs will be collected for a 1-hour observation period after study intervention administration.

AE = adverse event; AESI = adverse event of special interest; EDV = Early Discontinuation Visit; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential; β-hCG = beta human chorionic gonadotropin.

2 INTRODUCTION

2.1 Study Rationale

SARS-CoV-2 is an RNA virus capable of undergoing rapid mutations that have resulted in reduced responses to previously developed monoclonal antibodies (mAbs) used for c12 prevention and/or treatment. AZD3152 is a monoclonal antibody to the conservative epitope of SARS-CoV-2 spike protein and has a wide range of neutralizing activity against virus variants both previously prevalent and currently relevant.

RBD recognition by AZD3152 is mediated by multiple polar interactions of both heavy and light chains, along with hydrophobic interactions. The wide range of AZD3152 neutralizing activity results from the fact that this mAb binds to a highly conservative epitope that has remained unchanged among all known virus variants that used to circulate previously and CCI

AZD3152 is developed to ensure wide neutralizing activity against known SARS-CoV-2 VOCs for pre-exposure prophylaxis of COVID-19, resulting in the necessary level of protection regardless of any potential future mutations that may develop as the SARS-CoV-2 virus evolves.

An international phase I/III trial SUPERNOVA (NCT05648110) is ongoing to evaluate AZD3152 safety and neutralizing activity, in comparison with placebo and AZD7442 (EVUSHELD), as a pre-exposure prophylaxis method in adults and adolescents in the age of 12 years or above, with body weight of at least 40 kg.

This Phase II study will assess the safety, neutralizing activity and efficacy of AZD3152 in adults with immunocompromised conditions, including comorbidities contributing to weakened immunity, thereby increasing the risk of COVID-19 progression up to severe grade.

In the Russian Federation this is the only planned AZD3152 study that will provide clinical data on safety, neutralizing activity and efficacy in the target population of Russian participants. This study is legally required for AZD3152 marketing authorization in Russia.

While activity of previously authorized medications against new SARS-CoV-2 variants is decreasing, the need of innovative compounds that would significantly increase the variety of COVID-19 prevention methods is particularly high, and even more so – in the vulnerable population at risk of developing severe disease.

Evaluation and marketing authorization of AZD3152 will ensure Russian participants have access to the innovative compound designed for COVID-19 prophylaxis, allowing healthcare professionals gain experience with this medicine and use it as one of the tools to control diseases that jeopardize the community, which is relevant for the healthcare system in a setting when the activity previously authorized medicines against new SARS-CoV-2 variants is decreasing.

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 May 31, 2023, has caused over 767 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 decreased response to complete active immunization because of conditions/comorbidities that impair the immune system, resulting in reduced immune function (Alhumaid et al 2021, Harpaz et al 2016, Maltezou et al 2022, Parker et al 2022) or for whom vaccination is not suitable. SARS-CoV-2 mutations may cause a reduction in efficacy of currently available monoclonal antibodies (mAbs), which is why it is particularly relevant to develop new mAbs for COVID-19 prophylaxis for the population of high-risk disease progression to severe grades, due to the presence of conditions/comorbidities resulting in weakened immunity.

Neutralizing mAbs were developed and deployed to protect those who have a reduced immune response due to conditions / comorbidities affecting the immune system and those at risk of inadequate immune response to vaccination, with development of severe COVID-19. 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 (see sections above for more details). Such class of compounds may be used as a supplement to vaccination or other methods of prophylaxis.

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

Ongoing mutations of SARS-CoV-2 results in the emergence of variants of concern that have biologic characteristics determining increased infectivity, pathogenicity or reduced neutralizing activity of antibodies, including available on the Russian market EVUSHELD (AZD7442). Currently only omicron (PANGO B.1.1.529 line) is considered a VOC.

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 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 monoclonal antibodies. Alto results of pharmacokinetic modeling with regards to BA.1 and BA.1.1 confirm that after IM administration of 600 mg (rather than 300 mg) median EVUSHELD serum concentrations exceed the modeled values, consequently increasing the efficacy of the compound in the prophylaxis of disease caused by Omicron (see 4.3.2 for more details).

Novel monoclonal antibodies designed to prevent symptomatic COVID-19 must be able to neutralize all known SARS-CoV-2 viral variants and be resistant to further SARS-CoV-2 mutations. Such agents would provide an additional tool to mitigate individual risks, minimize outbreaks, and control the spread of disease. AZD3152 is being developed to provide efficacy similar to that of EVUSHELD but against a wider range of SARS-CoV-2 variants, including the ones for which a reduction of EVUSHELD neutralizing activity has been reported.

CCI [redacted]

AZD3152 bind to 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, conferring 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, reducing the potential risk of ADE disease. Incorporation of these amino acid substitutions did not alter the neutralization potency of EVUSHELD in vitro. CCI [redacted]

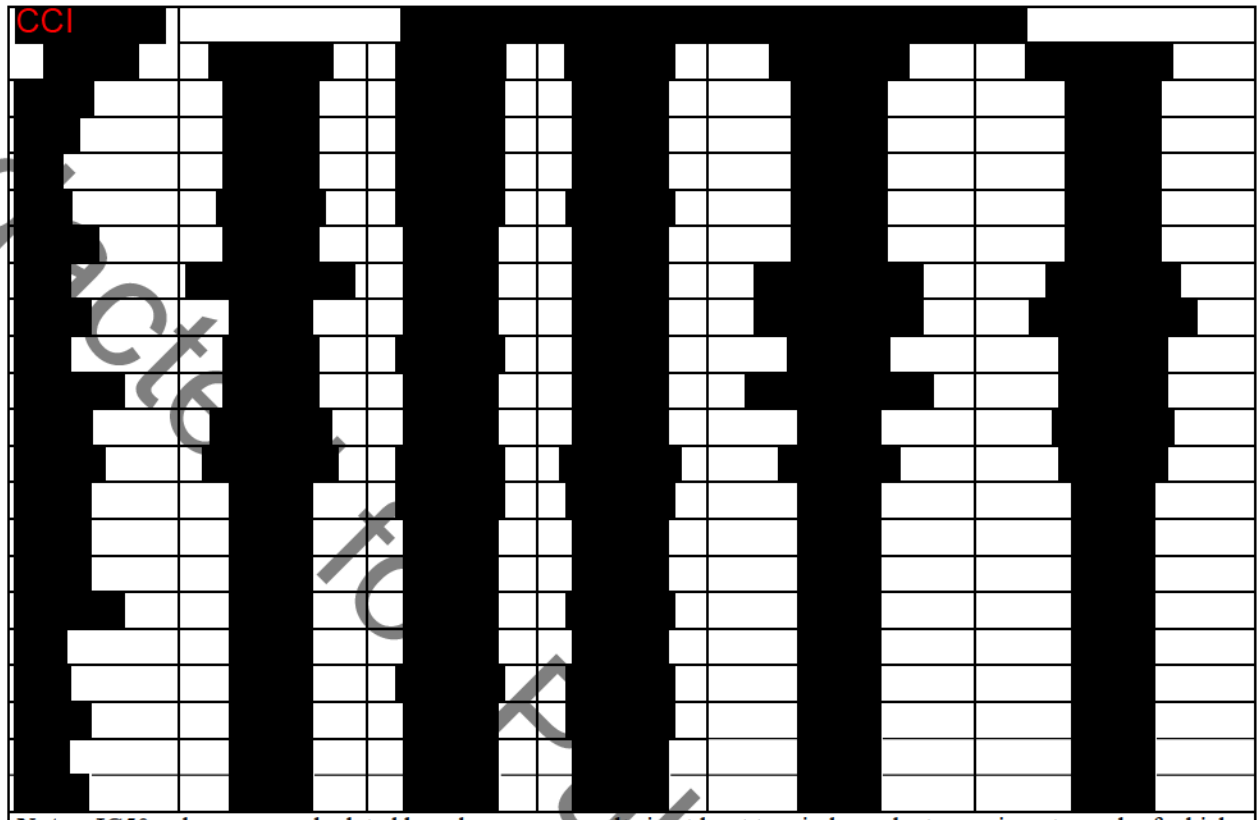
but EVUSHELD has wider efficacy against a broader range of SARS-CoV-2 variants of

concern.

AZD3152 efficacy for pre-exposure prophylaxis of COVID-19 is supported by the following evidence:

- The mechanism of action and PK of AZD3152 are similar to those of AZD7442 (EVUSHELD). CCI [redacted] Report on AZD3152 pharmacokinetics in transgenic mice expressing hFcRn as of June 14, 2022). Both agents bind to the epitopes of RBD on the spike protein, blocking its attachment to the human ACE2 receptor and preventing SARS-CoV-2 entry, resulting in its effective neutralization.
- 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 EVUSHELD (see Table 2). Currently the XBB.1 SARS-CoV-2 variant is predominant in the Russian Federation.
- 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), with relative risk reduction of 76.73, 95% CI 46.05, 89.96, $p < 0.001$, and is approved as EVUSHELD for the pre-exposure prophylaxis of COVID-19, and for treatment of COVID-19 in the Russian Federation, the EU and Japan.

Table 2 **Assessment of antiviral activity of cilgavimab, tixagevimab, AZD3152, AZD5156 and EVUSHELD in a pseudovirus neutralization assay**



Notes: IC50 values were calculated based on mean results in at least two independent experiments, each of which was conducted in three repetitive runs.
AZD1061 (cilgavimab, EVUSHELD component with a higher neutralizing activity against Omicron compared to tixagevimab)
IC50, Half maximal inhibitory concentration; mAb, monoclonal antibody.
Source: Study EVI5156-0005.

Subjects belonging to prioritized populations (see Provisional recommendations 2022), with high risk of severe COVID-19 (eg, individuals with immunocompromising conditions or comorbidities, including those taking immunosuppressive medications) or for whom vaccination is not suitable, will benefit most from AZD3152 administration for COVID-19 prophylaxis. It is noteworthy that currently XBB.1 is the predominant variant in the Russian Federation, and the investigational product has higher neutralizing potential against it, as compared to EVUSHELD (see Table 2).

The AZD3152 clinical trial program is presented below.

Table 3 List of completed, ongoing and planned clinical trials

Protocol	Status	Beginning	End	Phase	Expected number of subjects	Conducted in the Russian Federation
SUPERNOVA D7000C00001	Ongoing	December 2022	February 2025	I/III	3256	no
Little Dipper D7000C00004	Planned	April 2023	January 2025	I	48	no
D7000C00007	Planned	April 2023	August 2025	I	40	no
NOVELLA AZ-RU-00002	Planned	June 2023	April 2024	II	116	yes

Now SUPERNOVA (NCT05648110) Phase I/III global study is ongoing to evaluate the safety and neutralizing activity of AZD3152 in comparison with placebo and EVUSHELD for pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age or older weighing at least 40 kg. Participants of the SUPERNOVA study receive IM injections of AZD5156 (combination of AZD1061 [cilgavimab] and AZD3152) or placebo in the Sentinel Safety Cohorts, AZD3152 or placebo in the Main Cohort, and AZD3152 or EVUSHELD (AZD7442) in the Sub-study (will be considered as phase II). At the beginning of August, 2023, 1054 subjects have been enrolled, i.e. enrolment into the sentinel safety cohort (healthy volunteers, N=57) is complete and enrolment into the main cohort (immunocompromised patients) is ongoing.

. No safety concerns were noted based on review of the safety data from the Sentinel Safety Cohort (Day 29) after study intervention dose. Overall, this safety analysis of data from healthy participants in the Sentinel Safety Cohort supports moving forward into the Main Cohort of immunocompromised participants in the SUPERNOVA study.In the local study, AZD3152 is being evaluated for the pre-exposure prophylaxis of COVID-19 in adults with increased risk of inadequate immune response after vaccination (due to immunocompromising conditions including comorbidities that may contribute to weakened immunity), resulting in a high risk of severe COVID-19.

The results of this study will provide clinical data on safety and neutralizing activity of an innovation drug in the new region (the Russian Federation) will become an additional source of evidence supporting AZD3152 marketing authorization in the Russian Federation and will expand strategies for COVID-19 prophylaxis in a setting of continuous virus evolution.

A more detailed description of the chemistry, pharmacology, and nonclinical studies of AZD5156 and AZD3152 is provided in the Investigator's Brochure for AZD5156 and AZD3152.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

AZD3152 is a mAb directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. AZD3152 is a virus-specific monoclonal antibody without any known endogenous human target. There are no identified risks for AZD3152. The structural similarities between AZD3152 and EVUSHELD (AZD7442) components suggest similar safety profiles; modifications made for AZD3152 are not expected to have an effect on its safety, which is confirmed by an interim safety data review presented above.

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 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. 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. Such reactions were not reported in healthy volunteers who took part in the SUPERNOVA clinical trial.

For all mAbs, ADE of infection 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. Such abnormal condition is not expected with AZD3152 because, similar to EVUSHELD components, AZD3152 has 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. Such reactions were not reported in healthy volunteers who took part in the SUPERNOVA clinical trial.

CCI [redacted]

CCI [redacted]

2.3.2 Benefit Assessment

Non-clinical studies indicate that AZD3152 is effective against a wide range of SARS-CoV-2 variants; therefore, AZD3152 must ensure sufficient level of protection from COVID-19 in study subjects. 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 has shown in the Phase III PROVENT trial (Levin et al 2022), also suggesting AZD3152 protective potential.

Despite the rollout of effective SARS-CoV-2 vaccines, there remains an unmet medical need in an additional prophylaxis method that would provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging dominant variants, particularly in cases where the risk of mounting inadequate immune response to complete active immunization is expected (CDC 2021) (in which setting monoclonal antibodies are to be used as a supplementary protection method, beyond those already available), and those for whom vaccination is not suitable.

The individuals to be included in this study are adults having an increased risk for the development of severe COVID-19 due to reduced response to a complete course of active immunization and, therefore, compromised immunity, in who AZD3152 would ensure protection against COVID-19.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study (i.e. staying at the site under medical supervision within no less than 1 hours after drug administration, laboratory and instrumental examinations as per section 1.3, possible vaccination 29 days after the administration of investigational products), potential risks related to AZD3152 are outweighed by the expected benefits that may be available to subjects with an increased risk for inadequate response to active immunization and development of severe COVID-19. Furthermore, good safety of AZD3152 is confirmed by the safety results from the SUPERNOVA clinical trial in a sentinel cohort of healthy volunteers (n=57), consistent with phase I of clinical development. The collected data were consistent with further continuation of the clinical trial, proceeding to the second period – evaluation of AZD3152 efficacy and safety in the target population of immunocompromised patients (more than 1000 subjects have been randomized and dosed by now).

More detailed information about the known and expected benefits and potential risks of AZD3152/AZD5156 is provided in the corresponding Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Estimand Descriptions/Endpoints
Primary	
To evaluate the safety of AZD3152 compared with placebo	**Population:** Safety analysis set **Endpoints:** • Occurrence of AEs collected throughout the study • Occurrence of SAEs, MAAEs, and AESIs collected throughout the study **Intercurrent events:** Treatment policy will be applied, i.e., all events collected will be included in the analysis regardless of the presence and timing of intercurrent events. **Summary measure:** The number and proportion of subjects with AEs, SAEs, MAAEs, AESIs.
Secondary	
To compare the nAb responses to the SARS-CoV-2 emerging dominant variant(s) of concern circulating during the course of the study in serum following AZD3152 or placebo administration	**Population:** SARS-CoV-2 nAb analysis set **Endpoint:** Titer for SARS-CoV-2 emerging dominant variant(s) nAbs **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 this endpoint (i.e., while-on-treatment strategy is applied). **Summary measure:** Geometric mean titer (GMT) and geometric mean fold rise (GMFRs) (from baseline value through Day 29 after the single IM dose) of SARS-CoV-2 nAbs. Descriptive statistics for the log-transformed titer will include the number of participants, GMT and GMFR, corresponding gSD, 95% CI, minimum, and maximum and summarized by treatment arm.
To compare the incidence of symptomatic COVID-19 cases in participants receiving study intervention. (efficacy)	**Population:** Full analysis set **Endpoint:** Incidence of a post-treatment symptomatic COVID-19 case (negative RT-PCR at baseline to positive RT-PCR or positive antigen test at any time up

Objectives	Estimand Descriptions/Endpoints
	to 6 months AND symptoms specified in the modified WHO definition of symptomatic COVID-19). **Intercurrent events:** 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 have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied). **Summary measure:** incidence of a post-treatment symptomatic COVID-19 case.
Exploratory	
CCI [redacted]	**Population:** CCI [redacted] **Endpoints:** CCI [redacted] • CCI [redacted]
CCI [redacted]	CCI [redacted]

Objectives	Estimand Descriptions/Endpoints
	CCI [redacted]

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II study that will be conducted to evaluate the safety, neutralizing activity and efficacy of AZD3152. The study will enrol approximately 116 adults who have a reduced immune response due to a disease/condition affecting the immune system and who are at risk of developing an underdeveloped immune response to vaccination and developing severe forms of COVID-19.

Participants will be randomized 3:1 to receive AZD3152 (300 mg, 2 mL) or placebo (2 mL) administered IM in the anterolateral thigh on Day 1. A prerequisite for inclusion in this study is that participants have immunocompromised conditions, including comorbidities that may contribute to reduced immunity, which in turn increases their risk of progression to severe disease.

AZD3152 or placebo will be administered as a single IM injection in the anterolateral thigh.

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.

The study will be conducted at approximately 10 sites in the Russian Federation.

Adverse events, SAEs, MAAEs, and AESIs will be collected throughout the study. Immediate AEs will be collected for an1-hour observation period after study intervention administration. The duration of each participant's involvement in the study will be approximately 6 months from when the study intervention is administered.

If, following study intervention administration, a subject develops COVID-19, according to the Provisional recommendations on the methods for prevention, diagnosis and treatment of novel coronavirus infection (COVID-19), issued by the Ministry of Health of the Russian Federation, version 17 dated December 14, 2022 (Provisional recommendations 2022) (s)he must call "**122**" to be visited by a healthcare professional who, among other procedures, will perform a COVID-19 test. Once a visit by a healthcare professional has been requested, the subject must notify the study doctor of the date symptoms occurred and the date a healthcare professional visit has been requested, as soon as possible. Also, once a test result is available, the participant must report within 3 days the date of test and its result to the Investigator. If the test result is positive, the Investigator (or his/her delegate, according to the local regulations and institution guidelines) will make telephone calls ***every three days*** to collect safety data until the subject informs about his/her recovery.

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

Overall study design is described in Figure 1.

4.2 Scientific Rationale for Study Design

This study follows the design of exploratory phase II therapeutic trials. In accordance with the Board of Eurasian Economic Commission Recommendations, such studies may include parallel controls and comparison with baseline values, which applies to the design of this clinical trial. In accordance with the Board of Eurasian Economic Commission Recommendations such exploratory studies are of relatively short duration and are conducted with a small group of patients using surrogate or pharmacological endpoints or clinical indicators. In this study, the observation period and sample size are consistent with such parameters. In addition to assessing the safety of IP, the study also assesses its neutralizing activity against relevant variants of coronaviruses, which is the standard surrogate point for assessing efficacy in this class of drug for this indication.

Evaluation of safety and efficacy compared to placebo is a generally accepted approach in the early stages of clinical development of monoclonal antibodies (Decision of Council of the Eurasian Economic Commission November 3, 2016 №89 «Rules for conducting research on biological medicines in the Eurasian Economic Union»). This approach provides optimal comparative data for subsequent interpretation, is ethically justified and does not carry any additional risks in the conditions of a favourable change in the epidemic situation in the Russian Federation (in 2022, Rospotrebnadzor lifted restrictions imposed in connection with the pandemic). In addition, uneven inclusion in the study groups is planned – fewer participants will receive a placebo. All participants will be able to receive SARS-CoV-2 vaccines after the Day 29 assessments.

The overall study design is similar to the EVUSHELD (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 main difference from other study designs is the randomization ratio. Unequal randomization ratio will cover the need for additional safety information of AZD3152. Also, based on the available efficacy data, it is anticipated that participants in the AZD3152 arm will benefit more than participants in the placebo arm. AZD3152 is developing specially to prepare for future resistant mutations that may develop as the SARS-CoV-2 virus continues to evolve. The data obtained in previous studies suggests that the 6-month period following a single AZD3152 injection is adequate to meet the study objectives. The structural similarity between AZD3152 and the components of the EVUSHELD drug suggests a similar safety profile of AZD3152 to that of EVUSHELD; modifications made in the development of AZD3152 are not expected to affect the safety of the drug, which was confirmed in the sentinel cohort of clinical study SUPERNOVA (D7000C00001). At the time of assessment on day 29, no new safety data were identified, allowing further enrolment of patients in phase III. The primary endpoints are standard safety assessments.

Although the primary endpoint of the study is aimed at assessing safety, the study also aims to investigate the neutralizing activity against emerging dominant variants of SARS-CoV-2 and the efficacy of the drug. This study will help to identify a group of patients at high risk of developing severe COVID-19 who may benefit most from the drug administration.

The combination of objectives of this study is therefore consistent with the aim: to establish the

safety of an immunobiological medicinal product and its preventive efficacy for individuals with certain conditions or diseases that confer high risk of developing severe forms of COVID-19.

4.2.1 Rationale for Study Population

This study will involve adults 18 years of age or older who have conditions/comorbidities that may contribute to reduced immunity, which in turn increases their risk of progression to severe forms of disease. Due to the risk of developing an inadequate response to full vaccination due to immune system dysfunction due to existing conditions/comorbidities, administration of neutralizing mAb is also recommended for such individuals (Provisional recommendations, version 17 dated 24 December 2022; CDC 2020).

Age, comorbidities and immunosuppressive conditions, including the use of immunosuppressive therapy, are associated with the inadequate immune response to vaccination.

Immunological aging is an age-related dysregulation of the immune system, an age-related change in the components of the innate and adaptive immune system in the elderly, leading to impaired formation of protective immunity following immunization or infection (Poland et al 2018, Wagner and Weinberger 2020, Zimmermann and Curtis 2019).

Obesity has been shown to correlate with a weaker immune response to vaccines, which can also be considered a marker or state of immunosuppression. For example, obese people have reduced CD8+ T-cell activation compared to healthy people of normal weight (Poland et al 2018, Wagner and Weinberger 2020, Zimmermann and Curtis 2019).

Patients with chronic kidney disease are a priority group for vaccination, but the adequacy of the immunological response in this category of patients may not be high enough, and therefore booster vaccination is needed, as well as the use of prolonged viral neutralizing antibodies both as pre-exposure prophylaxis and as treatment (Provisional recommendations, version 17 of 24 December 2022).

Hippisley-Cox, et al. conducted a large-scale study on 6,952,440 vaccinated patients to develop and test risk prediction algorithms for COVID-19-related mortality and hospitalization in adult patients after one or two doses of COVID-19 vaccine. Mortality from COVID-19 has been shown to be 1.2 to 2 times higher in vaccinated patients who had chronic obstructive pulmonary disease (COPD) and/or cardiovascular disease (coronary heart disease, stroke, atrial fibrillation, heart failure, thromboembolism, peripheral vascular disease) (Hippisley-Cox, et al 2021). Thus, patients with these comorbidities also require the use of long-acting drugs containing viral neutralizing antibodies as pre-exposure prophylaxis

The study population most likely to benefit from receipt of IMP. The inclusion criteria are designed to select such individuals (for list of conditions, see Section 5.1).

4.3 Justification for Dose

4.3.1 Justification for AZD3152 Dose

The safety and tolerability of AZD3152 300 mg is being evaluated in the ongoing phase I/III SUPERNOVA study, preliminary safety profile is briefly described in section 2.2.2.

AZD3152 demonstrated effective in vitro neutralization as on live SARS-CoV-2 virus, with IC50 values obtained from CCI ng/mL (BA.1.1 variant) to CCI ng/mL (D614G variant), and on the pseudovirus of current variants of the SARS-CoV-2 virus, with the obtained IC50 values in the range from CCI ng/mL (XBB.1 variant) to CCI ng/mL (BA.2.75 variant). The newly identified circulating BQ.1.1 and XBB.1 variants are also neutralized by AZD3152 with IC50 values of CCI ng/mL and CCI ng/mL, respectively.

Based on non-clinical evidence it is predicted that administration of AZD3152 in a dose of 300 mg will maintain concentration of AZD3152 in the nasal epithelium lining fluid at above IC80 for such SARS-CoV-2 variants as BA.1, BA.1.1, BA.2, BA.4/5 BA.4.6, BQ.1, BQ.1.1, XBB.1 and BF.7 in at least 70% of study participants for greater than 6 months. The results of nonclinical studies evaluating the neutralizing activity of the molecule are presented in detail in "Module 2.6: Nonclinical pharmacological written summary". Drug substance: AZD3152 and AZD5156. Date: February 06, 2023.

4.3.2 Justification for Placebo

Evaluation of safety and efficacy compared to placebo is a generally accepted approach in the early stages of clinical development of monoclonal antibodies (Decision of Council of the Eurasian Economic Commission November 3, 2016 №89 «Rules for conducting research on biological medicines in the Eurasian Economic Union»). This approach provides optimal comparative data for subsequent interpretation, is ethically justified and does not carry any additional risks in the conditions of a favourable change in the epidemic situation in the Russian Federation (in 2022, Rospotrebnadzor lifted restrictions imposed in connection with the pandemic). In addition, uneven inclusion in the study groups is planned – fewer participants will receive a placebo.

CCI CCI is a safe and widespread placebo option in studies of parenteral dosage forms. A similar placebo option is used in the Main Cohort of ongoing Phase I/III global study (SUPERNOVA, NCT05648110).

Placebo will be administered similarly to the AZD3152: single IM (thigh) injection of 2 mL.

4.4 End of Study Definition

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.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be 18 years of age or older at the time of signing the informed consent.
2. Written informed consent obtained from the participant prior to performing any protocol-related procedures, including screening evaluations.
3. Negative rapid antigen test SARS-CoV-2 at Visit 1.
4. Weight ≥ 45 kg at Visit 1.
5. Adult participants at increased risk of progression to severe forms of disease due to immunosuppressive diseases/conditions (Furer et al 2020, Poland et al 2018, Wagner and Weinberger 2020, Zimmermann and Curtis 2019), having at least 1 of the following risk factors:
    - Obese, ie, BMI ≥ 30
    - Congestive heart failure
    - Chronic obstructive pulmonary disease
    - Chronic kidney disease, ie, GFR < 30 mL/min/1.73 m^2 (Lamb et al 2013)
    - Intolerant of vaccine. Defined as previous history of severe adverse event or serious adverse event after receiving any approved vaccine.
    - Immunocompromised state (must satisfy at least 1 of the following risk factors at enrollment)
        a) 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
        b) 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)
        c) 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)
        d) Received chimeric antigen receptor T-cell therapy

e) Within 1 year of receiving B-cell depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, alemtuzumab)

f) Have a moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immune deficiency, 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. 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:

- Women 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.
- All female participants of childbearing potential must have a negative urine pregnancy test result at screening.
- 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.
- 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® or their equivalents.
- 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.

8. Able to understand and comply with all study requirements/procedures, based on the assessment of the Investigator.

5.2 Exclusion Criteria

Participants are excluded from the study 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) 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 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 6 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 6 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. 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.

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/AZD5132 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 above Sections.
- 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) utilised by a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

ASTRAZENECA AB will supply LLC AstraZeneca Pharmaceuticals AZD3152, solution for intramuscular injection, at a dosage of 150 mg / ml, 2 ml in a vial, as investigational drug in a standard package "IN BULK".

Further secondary packaging, labelling and release of IMP, will be carried out on territory of the Russian Federation by Manufacturing site and by Sponsor, in accordance with applicable regulations.

Placebo CCI [redacted]

Participants will be randomized to receive AZD3152 or placebo (3:1 ratio). There is no cap for randomization in each group to be implemented on site level of each investigational product, because it will increase overage of IMP for trial conduction. Details of these study interventions are presented in Table 5 and are described below.

Each vial of AZD3152 contains colourless to slightly yellow, clear to opalescent solution for injection. Label-claim volume per vial is 2 ml.

A placebo CCI [redacted] is colourless, clear solution for injection. CCI [redacted]

AZD3152 or placebo will be administered as a single IM injection in the anterolateral thigh.

If a participant experiences an immediate hypersensitivity reaction after receipt of the IM injection, appropriate necessary treatment should be prescribed. For details on the treatment of anaphylactic reactions after study intervention IM injections see Appendix E.

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.

Table 5 Investigational Products

Intervention name	AZD3152	PLACEBO
Type	Drug	Placebo
Dose formulation	AZD3152 will be supplied as a single vial. AZD3152 vial contains 300 mg solution for injection. The solutions contain 150 mg/mL of AZD3152 in CCI [redacted]	Placebo is CCI [redacted]
Unit dose strength(s)	300 mg AZD3152 at 150 mg/mL	CCI [redacted]
Dosage level(s)	300 mg single dose of AZD3152	single dose of 2 mL
Route of administration[c]	1 IM injection (thigh) of 2 mL of AZD3152	1 IM injection (thigh) of 2 mL of placebo
Use	Investigational	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	AstraZeneca	CCI [redacted]

Packaging and labelling	IMP will be provided in glass vials. Each glass vial will be labelled as per country requirement.	CCI [redacted]

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

6.2 Preparation/Handling/Storage/Accountability

- IMP vials/ampoules are stored at 2°C to 8°C 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) and in accordance with applicable regulatory requirements.
- A temperature log will be used to monitor the storage conditions of IMP in 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 or refrigerator. 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. Use of study intervention for which a temperature deviation has been identified will not be permitted prior to AstraZeneca's notification.
- Only participants enrolled in the study may receive study intervention and only authorised 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 labelled storage conditions with access limited to the Investigator and authorised 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).

- Further guidance and information for the final disposition of unused study interventions, detailed dose preparation, handling, and administration information will be provided in the Investigational Product Handling Manual.

The doses of AZD3152 and placebo for administration must be prepared by the Unblinded 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 between retrieval of the drug from the vial/ampoule into the syringe and the start of administration must not exceed:

- 24 hours at 2°C to 8°C
- 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/ampoules (that is, the individual storage time limits are not additive). AZD3152 and placebo do not contain preservatives; any unused portion of the vial/ampoule must be discarded immediately after use.

6.3 Measures to Minimise Bias: Randomization and Blinding

6.3.1 Randomization

The participants will be randomized to receive AZD3152 or placebo (3:1 ratio).

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, IWRS access and instruction will be provided to each site. Study intervention will be administered at the Visit 1.

The IWRS 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 IWRS user manual that will be provided to each center.

6.3.2 Blinding

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 AZD3152 and placebo are visually distinct prior to dose preparation (due to differences in appearance), 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. Personnel preparing and administering study intervention may be the same individual. 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 labelling of IMP
- Those generating the randomization list and IWRS system
- The AstraZeneca Alliance Team members responsible for supply chain
- Unblinded AstraZeneca designees (if applicable)
- Unblinded pharmacist
- Staff of bioanalytic laboratory
- The unblinded team(s) (to be specified in the Study Integrity Plan) for interim analysis at AstraZeneca and/or its delegate.

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 IWRS will be programmed with blind-breaking function. Unblinding should only occur within the IWRS 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 therapy can be unblinded by 41 authorized representatives of the study site. 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 event 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 unblinded pharmacist or designee. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

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 enrolment 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.

Table 6 lists the permitted and restricted, medications during the study.

Table 6 Permitted, Restricted, and Prohibited Medications

Use Category	Type of medication/treatment	Timeline/instructions
Permitted	Routine vaccines except SARS-CoV-2 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 administration 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 immune deficiency	Allowed. If possible, administration of immunoglobulin should be avoided on the same day as study intervention.
	Participants may take concomitant medications prescribed by their healthcare provider for management of chronic medical conditions and/or for health maintenance. Healthcare provider 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	

Use Category	Type of medication/treatment	Timeline/instructions
	according to local standard of care (which will be recorded as concomitant medication), including investigational agents outside a clinical trial setting.	
Prohibited	None	None
Restricted	Blood/plasma donation	Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after study intervention administration, ie, 15 months.
	SARS-CoV-2 vaccines	SARS-CoV-2 vaccines should not be given within 6 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 as well as 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 Visit 1 and until 6 months after the dose of IMP.

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 will receive a single dose of study intervention (AZD3152 or placebo). If a participant experiences an immediate hypersensitivity reaction after receipt of the IM injection, 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.

The study may be stopped if, in the judgment of AstraZeneca, trial participants are placed at

unnecessary risk because of clinically significant findings that:

1. meet individual stopping criteria or are otherwise considered significant
2. are assessed as causally related to study drug,
3. are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the participants at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the participants' interests.

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 format (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 Study Intervention 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).

A participant who considers withdrawing from the study should always be asked about the reasons and the presence of any AE. The investigator will follow up AEs outside of the clinical study.

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 Sponsor.

If the participant withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawal subjects will not be replaced.

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 enrolment of the participants) 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.

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 investigational product. 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. 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.

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 visits specified in the SoA (Table 1). Authorized laboratory will measure nAbs to the SARS-CoV-2 emerging dominant variant(s) circulating during the course of the study, using validated live virus neutralization assays.

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 (adapted from the WHO COVID-19 case definition as defined by WHO 2022 in Clinical management of COVID-19: living guideline) from the past week.

The following criteria adapted from the WHO COVID-19 case definition clinical criteria (WHO 2022):

- Any two of the following: fever (subjective definition to be used for 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 (subjective definition to be used for 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.

If, following study intervention administration, a subject develops COVID-19, according to the Provisional recommendations on the methods for prevention, diagnosis and treatment of novel coronavirus infection (COVID-19), issued by the Ministry of Health of the Russian Federation, version 17 dated December 14, 2022 (Provisional recommendations 2022) (s)he must call "122" to be visited by a healthcare professional who, among other procedures, will perform a COVID-19 antigen test or RT-PCR. Once a visit by a healthcare professional has been requested, the subject must notify the study doctor of the date symptoms occurred and the date a healthcare professional visit has been requested, as soon as possible. Also, once a test result is available, the participant must report within 3 days the date of test and its result to the Investigator. If the test result is positive, the Investigator (or his/her delegate, according to the local regulations and institution guidelines) will make telephone calls ***every three days*** to collect safety data until the subject informs about his/her recovery.**Safety Assessments**

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

8.2.1 Physical Examinations

Full and targeted physical examinations will be performed at the visits 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 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 pulse rate, respiratory rate, blood pressure (on a non-dominant arm after a 10-minute rest in a sitting position), and body temperature will be assessed at the visits as specified in the SoAs (Section 1.3). On the visit 1 day 1, vital signs will be assessed pre-dose and again approximately 10 to 15 minutes after the second injection is given.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

8.2.3 Electrocardiogram

12-lead electrocardiogram will be performed at timelines as specified in the SoA (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.

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.

8.2.4 Clinical Safety Laboratory Assessments

The serum chemistry, haematology, and coagulation analyses will be performed at a local laboratory at or near to the study site (see Section 1.3.1). Blood should be taken in the morning on an empty stomach, after 8-14 hours of overnight fast.

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 7.

Table 7 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, high-sensitivity test (screening only)
Glucose (random)	
Coagulation	
Activated partial thromboplastin time (aPTT)	Prothrombin time (PT) (or international normalized ratio)
Other	
HIV test (all subjects)	
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 WOCBP only, a urine or serum β-hCG pregnancy test will be performed locally at Visit 1. The test must be negative before dosing. 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 will be recorded.

Injection site reactions will be monitored as specified in the SoAs (Section 1.3). On study day 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 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

AEs, MAAE, AESI will be collected from the time of study intervention administration throughout the study, up to and including the last visit.

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

Any AESIs will be specified in the eCRF by Investigator and will be assessed from the time of study intervention (see Section 8.3.4).

If the Investigator becomes aware of an AE/SAE with a suspected causal relationship to the study intervention that occurs after the data collection period specified in the protocol, or after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, but not late than 24 hours, 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 Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(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
- Description

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 investigational product?'

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 AESIs will be specified in the eCRF by Investigator 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 are:

- CCI
- [redacted]

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 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 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 summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product 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, anaemia versus low haemoglobin 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 and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ 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 a 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 document for definition of expectedness/listedness is the AZD3152/AZD5156 Investigator's Brochure.

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 adverse event unless there is a suspicion that the investigational product under study 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 can be found in Appendix BB 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 can be found in Appendix BB 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 can be found in Appendix BB 4.

In this study participants will receive investigational products administered IM in the anterolateral thigh on Day 1. All participants will be dosed at the site, they will receive study intervention directly from the unblinded pharmacist or designee, under medical supervision. The chance for drug abuse and drug misuse by participant is rare.

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 5).

- 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 one 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 for central assessment 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 a Clinical Study Report in line with consent and local requirements, after which they will be destroyed/repatriated.

8.5.1 CCI

CCI [redacted]

8.5.2 SARS-CoV-2 Neutralizing Antibodies

Neutralizing antibody titers against SARS-CoV-2 will be evaluated using a validated live neutralization assay. Samples for the assessment of neutralizing antibody titers against SARS-CoV-2 should be collected per the SoAs (Section 1.3.1). At each visit 2 aliquots should be collected: main and back up.

8.5.3 CCI

[redacted] CCI [redacted]

8.5.4 Pharmacodynamics

Pharmacodynamics will not be evaluated.

8.5.5 Virologic Assessments

At Visit 1, a rapid test for SARS-CoV-2 antigens will be performed at the study sites to assess inclusion criteria, materials for the test will be provided by AstraZeneca. Sample collection and

assay procedure will be carried out according to the instructions enclosed in the commercial rapid test kit.

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

9.1 Statistical Hypotheses

The primary objective of the study is to evaluate the safety of AZD3152 compared with placebo. No formal statistical hypothesis was proposed, and the data presentation and analysis will be descriptive in its nature.

9.2 Sample Size Determination

The primary objective of the study is to evaluate the safety of AZD3152 compared with placebo. Corresponding primary endpoints to be examined:

- Occurrence of AEs collected throughout the study
- Occurrence of SAEs collected throughout the study
- Occurrence of MAAEs collected throughout the study
- Occurrence of AESIs collected throughout the study

Sample size determination is based on the probability-based approach for a single event. The probability of adverse event is *p*, therefore, the probability of no adverse event is *(1 – p)*.

The probability of no observations in n observations = *(1 – p)^n*, and this probability is equal to *(1 - power)*. We need to solve an equation: *(1 – p)^n = (1 – power)* which is equal to *n*log10(1 – p) = log10 (1 – power)*.

Solving for n, we get: *n = log10 (1 – power) / log10(1 – p)*

The choice of the CCI **threshold of AE rates** was based on the data from PROVENT study (D8850C00002/NCT04625725). The study was performed in similar population. Safety information used for the calculation was collected during a minimum of 5-month safety follow-up in all participants and a median duration of follow-up was approximately 6 months, which is equal to the planned observation period in the current study, additional safety data (collected for the longer follow-up period) in the final study report for PROVENT study was quite similar to what is collected at 5-month safety follow-up. In PROVENT study the frequencies of **SAE** were low: CCI in mAb (EVUSHELD) group and CCI in placebo group. Percentages of subjects experienced at least one **AESI** (anaphylaxis and other severe hypersensitivity reactions

and reactions at the site of injection) were also low and comparable both in mAb and placebo groups CCI respectively). Therefore, **the lowest frequency among all categories of safety events in active therapy arm** (in participants in the EVUSHELD group) **was reported as** CCI For sample size calculation in local study the CCI **threshold of AE rates** was used as clinically justified, because it will be sufficient to detect the rarest important AEs (SAEs, AESIs) in AZD3152 arm.

If the target power for AZD3152 group would be 80%, the equation to solve is

CCI

The arm in which CCI subjects will receive AZD3152 will allow for the recognition of AEs occurring at a frequency of CCI or higher with CCI power. With randomization at 3:1 ratio, we should include not less than 108 participants (CCI subjects in AZD3152 group and CCI in placebo group). Thus, with expectation that drop-out rate will be around 5%, we should randomize **116 participants** CCI **subjects in AZD3152 arm and** CCI **in placebo arm**).

9.3 Populations for Analyses

The following populations are defined:

Table 8 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 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 post-dose antibody measurements (i.e. at least one post-dose antibody measurement with a measurable SARS-CoV-2 titer in serum). Participants will be classified according to the actual received treatment. 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.

9.4 Statistical Analyses

The statistical analysis plan will be finalized before conducting an interim analysis based on data in 116 subjects during the follow-up period of 29 days after administration of study intervention.

This section contains all the main features of the proposed analysis of the primary and secondary endpoints and how issues encountered in the analysis will be managed. Given the exploratory nature of the study, the section provides more general principles and guidance for some variables.

9.4.1 General Considerations

Categorical variables will be presented as frequencies and proportions in percent. Continuous variables will be presented as means, geometric means (where applicable), standard deviations, geometric standard deviations (where applicable), medians, minimum and maximum, and quartiles (where applicable), with number of observations. When necessary, means and geometric means will be provided with two-sided 95% confidence intervals (CI). Treatment arms will be descriptively compared by corresponding variables.

The data and results of the analyses will be presented in the form of tables as well as listings, sorted by treatment arms and participant numbers. Methods of analysis will be outlined in detail in the Statistical Analysis Plan.

Validated SAS software version 9.4 or R statistical package version 4.2 or higher will be used for statistical analysis and reporting of the study data. The results of the analysis presented in the clinical study report will be validated according to the company's standard operating procedures.

9.4.2 Endpoints

9.4.2.1 Primary Endpoint

Primary safety endpoint includes AEs and SAEs, MAAEs, and AESIs collected throughout the study. 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 severity and relationship to study intervention as judged by the Investigator.

Intercurrent events: treatment policy will be applied, i.e., all events collected will be included in the analysis.

Safety analysis set will be used for the analysis of this endpoint.

Number and proportion of participants with AEs, SAEs, MAAEs, and AESIs (occurring throughout the study period after study intervention administration) separately will be provided for each arm, and will be descriptively compared between arms.

9.4.2.2 Secondary Endpoint(s)

Secondary endpoint: **Titer for SARS-CoV-2 emerging dominant variant(s) nAbs.**

Corresponding endpoints are GMTs and GMFTs for SARS-CoV-2 emerging dominant variant(s) nAbs.

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 this endpoint (i.e., while-on-treatment strategy is applied).

SARS-CoV-2 neutralizing antibody analysis set will be used for the analysis of this endpoint.

Descriptive statistics for the log-transformed titer will include the number of participants, GMT and GMFR, corresponding gSD, 95% CI, minimum, and maximum and summarized by treatment arm, visit and optionally by virus variant.

The dominant SARS-CoV-2 variants circulating during the study will be identified by the time of analysis.

Summary measures for nAb responses against the emerging dominant variant circulating during the course of the study will be presented as GMT and GMFR at each scheduled visit involving collection of the relevant biosamples.

GMT and GMFT will be descriptively compared between treatment arms.

Secondary endpoint: **incidence of a post-treatment symptomatic COVID-19 case** (negative RT-PCR at baseline to positive RT-PCR or positive antigen test at any time up to 6 months AND symptoms specified in the modified WHO definition of symptomatic COVID-19).

Intercurrent events: 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 have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied).

The numbers and percentages of symptomatic COVID-19 cases up to 6 months will be presented. Treatment arms will be descriptively compared by corresponding variables.

9.4.2.3 CCI

[redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

9.4.3 Safety

These data will be presented using safety analysis set.

Adverse events will be coded using the most current version of MedDRA, where possible. They will be summarised by system-organ class, preferred term, severity and relationship to the study intervention as assessed by the Investigator.

Adverse events will be presented as frequencies and percentages of participants with reported AEs for each system-organ class (SOC) and preferred term (PT) in the tables by treatment groups:

- Overall table for AEs;

- AEs by SOC and PT, with additional breakdown by relationship to the study intervention;

- AEs by SOC and PT, with additional breakdown by grade 3 or higher according to CTCAE;

- SAEs by SOC and PT, with additional breakdown by relationship to the study intervention;

- MAAEs by SOC and PT, with additional breakdown by relationship to the study intervention;

- AESIs by SOC and PT, with additional breakdown by relationship to the study intervention;

- Additional tables can be planned and detailed in the Statistical Analysis Plan.

Laboratory values will be presented in tables with descriptive statistics by treatment arms for each visit for measured values and for each visit after study intervention administration for changes relative to baseline values. There will also be tables of shifts relative to norms for each parameter for each treatment arm.

Vital signs as well as electrocardiogram (ECG) results will be presented in tables with descriptive statistics by treatment arm for each visit for the measured values and for each visit after study intervention administration for changes relative to the initial values.

All safety parameter data will be presented in the listings.

9.5 Interim Analyses

Interim analysis (unblinded)

An interim analysis is planned after 116 participants have completed Visit 4 visit 4 (Day 29) (or early withdrawal from the study) to evaluate early safety at Day 29. Efficacy data may be presented as appropriate at interim analysis if adequate data allows.

This interim analysis will include primary endpoint variables: all AEs, SAEs, MAAEs, and AESIs and nAb responses to the SARS-CoV-2 emerging dominant variant(s).

This interim analysis will be unblinded and will be performed by a separate unblinded team. All the parameters, along with other results (disposition, demographic data etc. – to be specified in the SAP) will be provided by treatment arms. Treatment arms will be descriptively compared by corresponding variables.

Final analysis (unblinded)

The final analysis will be performed once all subjects complete Visit 6 (Day 181) or early withdrawal from the study.

Results of exploratory endpoint evaluation may be presented in a clinical study report or in a separate report.

The Statistical Analysis Plan will describe both planned analyses in more detail.

The study will maintain a double-blinded (i.e., blind for participants and Investigators/site staff) until the final analysis. To maintain the integrity of the study to allow 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 interim 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. Participant-level unblinding information will be kept strictly confidential, and the rationale for any unblinding will be documented.

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 Good Clinical Practice (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 authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO 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 ICH guidelines, the IRB/IEC, 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) 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 or state other documents] 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 sub-Investigators 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 authorised representative and answer all questions regarding the study.
- Participants 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.
- 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 authorised 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 authorised 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 authorised 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 authorised

personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

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 the Monitoring Plan.
- 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 ongoing source data verification to confirm that data entered into the eCRF by authorised 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 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 multicentre 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 adverse event 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 unfavourable 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

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 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 jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** 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 judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, 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 a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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 judgement 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 jeopardise 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 judgement 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 anaemia 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 aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- 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 recognised 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 AstraZeneca study intervention 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 intercepted before the participant received the drug.
- Did not occur, but circumstances were recognised 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 IWRS errors).
- Wrong drug administered to participant (excluding IWRS errors).

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

- Errors related to or resulting from IWRS - 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)

In this study participants will receive investigational products administered IM in the anterolateral thigh on Day 1. All participants will be dosed at the site, they will receive study intervention directly from the unblinded pharmacist or designee, under medical supervision. The chance for drug abuse and drug misuse.

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.

In this study participants will receive investigational products administered IM in the anterolateral thigh on Day 1. All participants will be dosed at the site, they will receive study intervention directly from the unblinded pharmacist or designee, under medical supervision. The chance for drug abuse and drug misuse by participant is rare.

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 centre keeps full traceability of collected biological samples from the participants while in storage at the centre 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 analysed, 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

LABELLING 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 Adverse Event 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. 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 (ALP).

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 ALP 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:

- Inform the AstraZeneca representative that the participant has met PHL criteria.
- 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 Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to 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.
  - 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 TBL) 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 Study 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 Potential Hy's Law 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 Potential Hy's Law, (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. The list may be modified based on clinical judgment. Any test results need to be recorded.

Hy's Law Lab Kit for Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	CD-transferrin
Autoimmune hepatitis	ANA Anti-LKM ASMA
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin 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) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

To assist with the mitigation of these AEs, see Table 9, 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 9 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) 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	Evaluate participant, including close monitoring of vital signs. At the discretion of the Investigator, treat participant, for example, with: Localized cold pack or heat to the injection site. If more generalized reaction:	Pause or hold additional study intervention injection immediately. At the discretion of the Investigator, resume current study intervention administration under observation.

Severity of Symptoms	Treatment	Study Intervention
site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mm Hg change in systolic BP from pre-administration measurement.	• Diphenhydramine 50 mg PO or equivalent and/or • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or • Topical antihistamines and/or low-potency topical corticosteroid preparations and/or • Anti-nausea medication, as needed.	
Moderate reactions (during or immediately post injection) 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. Treat participant, for example, with: • Normal saline (~500 to 1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or • Anti-nausea and/or antiemetic intramuscular, as needed.	Stop or hold additional study intervention administration immediately. At the discretion of the Investigator, resume current study intervention administration under observation.
Moderate hypersensitivity reactions 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. Treat participant, for example, with: • Normal saline (~500 to 1000 mL/hour IV) and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg.	Stop study intervention administration immediately
Severe Above plus fever with rigors, hypo- or hypertension with	Evaluate participant, including close monitoring of vital signs.	Stop study intervention administration immediately. Do not resume current dosing.

Severity of Symptoms	Treatment	Study Intervention
≥ 40 mm Hg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope, incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor OR **Life-threatening** 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	Maintain airway, oxygen if available. Treat participant immediately, for example with: • Normal saline (~500 to 1000 mL/hour IV) • 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 • IV corticosteroids, such as hydrocortisone 100 mg or methylprednisolone 20 to 40 mg • Diphenhydramine 50 mg IV or equivalent • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator. Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine Grade 4 event At the discretion of the Investigator	Permanently discontinue study intervention administration. 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
ADE	Antibody dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C1q	Complement component 1q
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European union
EUA	Emergency use authorization
FAAN	Food allergy and anaphylaxis network
FAS	Full analysis set
Fc	Fraction crystallizable
FcRn	Neonatal Fc receptor
GCP	Good clinical practice
GMFR	Geometric mean fold rise (GMT ratio of post-treatment titer to baseline titer)
GMT	Geometric mean titer
gSD	Geometric standard deviation
HIV	Human immunodeficiency virus
HL	Hy's law
IC_{xx}	Concentration required for XX% inhibition

Abbreviation or special term	Explanation
ICF	Informed consent form
ICH	International council for harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IL-D	Illness day
IM	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional review board
IWRS	Interactive web response system
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	Non-investigational medicinal product
NIV	Non-invasive ventilation
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
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
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

Abbreviation or special term	Explanation
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 Forms of Early Safety Data Review (ESDR) Decision by the Safety Assessment Committee in the SUPERNOVA Study

These forms are appended as separate documents.

Appendix H Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

11 REFERENCES

Alhumaid et al 2021

Alhumaid S, Al Mutair A, Al Alawi Z, Rabaan AA, Tirupathi R, Alomari MA, et al. Anaphylactic and nonanaphylactic reactions to SARS-CoV-2 vaccines: a systematic review and meta-analysis. Allergy Asthma Clin Immunol 2021;17(1):109.

Bosch et al 2003

Bosch BJ, van der Zee R, de Haan CAM, Rottier PJM. The coronavirus spike protein is a class I virus fusion protein: Structural and functional characterization of the fusion core complex. J Virol. 2003;77:8801–11.

Case et al 2022

Case JB, Mackin S, Errico J, Chong Z, Madden EA, Whitener B, et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains. Nat Commun. 2022;13(1):3824.

CDC 2021

CDC (Centers for Disease Control and Prevention). General Best Practice Guidelines for Immunization: Altered Immunocompetence. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html. Accessed 23 May 2022.Dall'Acqua et al 2006

Dall'Acqua WF, Kiener PA, Wu H. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). J Biol Chem 2006;281(3): 23514-24.

Fact Sheet EUA Bebtelovimab 2022

US Food and Drug Administration. Fact Sheet For Healthcare Providers: Emergency Use Authorization for Bebtelovimab, March 2022. Available at: https://www.fda.gov/media/156152/download. Accessed 23 May 2022.

Furer et al 2020

Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(1):39-52.

Gupta et al 2021

Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early Treatment for Covid-19 with Sars-Cov-2 Neutralizing Antibody Sotrovimab. N Engl J Med 2021;385:1941-50.

Harpaz et al 2016

Harpaz R, Dahl RM, Dooling KL. Prevalence of Immunosuppression Among US Adults, 2013. JAMA 2016;316(23):2547-8.

Hoffmann et al 2020

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.

Lamb et al 2013

Lamb EJ, Levey AS, Stevens PE. The Kidney Disease Improving Global Outcomes (KDIGO) guideline update for chronic kidney disease: evolution not revolution. Clin Chem. 2013;59(3):462-5.

Levin et al 2022

Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. N Engl J Med 2022;386(23):2188-2200.

Li 2016

Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016;3:237–61.

Loo et al 2022

Loo YM, McTamney PM, Arends RM, Abram ME, Aksyuk AA, Diallo S, et al. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in nonhuman primates and has an extended half-life in humans. Sci Transl Med 2022;14(635):eabl8124.

Lusvarghi et al 2022

Lusvarghi S, Pollett SD, Neerukonda SN, Wang W, Wang R, Vassell R, et al. SARS-CoV-2 BA.1 variant is neutralized by vaccine booster-elicited serum, but evades most convalescent serum and therapeutic antibodies. Sci Transl Med 2022;14(645):eabn8543.

Maltezou et al 2022

Maltezou HC, Anastassopoulou C, Hatziantoniou S, Poland GA, Tsakris A. Anaphylaxis rates associated with COVID-19 vaccines are comparable to those of other vaccines. Vaccine 2022;40(2):183-6.

NIH 2017

NIH. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Published 2017. Accessed 23 May 2022.

Oganesyan et al 2008

Oganesyan V, Gao C, Shirinian L, Wu H, Dall'Acqua WF. Structural characterization of a human Fc fragment engineered for lack of effector functions. Acta Crystallogr D Biol Crystallogr. 2008;64(Pt 6):700-4.

Parker et al 2022

Parker EK, Desai S, Marti M, Nohynek H, Kaslow DC, Kochhar S, et al. Response to additional Covid-19 vaccine doses in people who are immunocompromised: A rapid review. Lancet Glob Health 2022;10(3):e326-e28.

Poland et al 2018

Poland GA, Ovsyannikova IG, Kennedy RB. Personalized vaccinology: A review. Vaccine. 2018;36(36):5350-7.

Sampson et al 2006

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Tuekprakhon et al 2022

Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, Zhou D, Ginn HM, Selvaraj M, et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. Cell. 2022;185(14):2422-33

Wagner and Weinberger 2020

Wagner A, Weinberger B. Vaccines to Prevent Infectious Diseases in the Older Population: Immunological Challenges and Future Perspectives. Front Immunol. 2020;11717.

Walls et al 2017

Walls AC, Tortorici MA, Snijder J, Xiong X, Bosch BJ, Rey FA, et al. Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion. Proc Natl Acad Sci U.S.A. 2017;114:11157–62.

Weinreich et al 2021

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. Regn-Cov2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2021;384:238-51.

WHO 2020

World Health Organization. WHO COVID-19 Case definition, December 2020. Available at: https://apps.who.int/iris/rest/bitstreams/1322790/retrieve. Accessed 22 September 2022.

WHO 2023

WHO Coronavirus disease (COVID-19) dashboard. Available at: https://covid19.who.int. Accessed 05 June 2023.

WHO Working Group 2020

WHO Working Group on the Clinical Characterisation and Management of COVID-19

infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20(8):e192-7.

Zimmermann and Curtis 2019

Zimmermann P, Curtis N. Factors That Influence the Immune Response to Vaccination. Clin Microbiol Rev. 2019;32(2).