Clinical Study Protocol Addendum	
IMP	AZD7442
Study Code	D8850C00002
Sub-study Code	D8850C002A01
Version	Amendment 2.0 USA
Date	13 June 2022

A Phase III Multi-center, Open-label Sub-study in Adults to Assess the Safety, PK, and Immunogenicity of Repeat Doses of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061) (The PROVENT Repeat Dose Sub-study)

Sponsor Name: AstraZeneca AB

Legal Registered Address: PPD

Regulatory Agency Identifier Number(s): IND Number: 150712
EudraCT Number: 2020-004356-16

This Clinical Study Protocol Addendum 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 AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 2.0 [USA Amendment 1] of CSP Addendum	13 June 2022
Version 10.0 [Amendment 9] of Original CSP Original CSP Addendum [Version 1.0]	01 December 2021

Version 2.0 [USA Amendment 1] of CSP Addendum, 10 June 2022

Key amendment and rationale for change:

The protocol was amended for the following reasons:

1 Ongoing discussions with the Agency regarding emergency use authorization redosing.

2 To collect data for the dosing regimen (600 mg every 6 months). Discussions regarding this dosing regimen have been ongoing with FDA for EUA.

3 In response to FDA comments received on the protocol in November 2021, where AstraZeneca responded that the CSP will be updated in a future amendment to include additional repeat dosing beyond the second dose once additional data are available to inform the recommended dose interval.

Based on clinical data from the Phase III PROVENT parent study (Study D8850C00002), the CSP addendum for the PROVENT sub-study (Study D8850C002A01) has been updated from Version 1.0 (Original CSP addendum, dated 01 December 2021) to Version 2.0 (dated 13 June 2022) to include a dosing group who will receive additional repeat doses of 600 mg AZD7442 at the recommended dosing interval.

By preparing for new and future SARS-CoV-2 variants of concern (i.e., BA.4 and BA.5 currently increasing in prevalence) this protocol is being updated to include a 600 mg dose with an administered frequency of 6 months over 12 months to maintain the efficacy. The 600 mg IM dose selected for this sub-study extension is based on the 600 mg dose administered in the TACKLE study, and 600 mg AZD7442 is authorized for emergency use in the USA since 24 February 2022; both of which demonstrated a generally safe and well-tolerated safety profile.

Group level recruitment caps may be placed to ensure 50 or more participants complete the study with their assigned dose and valid samples. Approximately 150 participants from the USA may be selected from the existing participants enrolled on the sub-study with an approximately even distribution coming from the 2 existing groups to receive repeat doses

of 600 mg IM. This approach will maintain a balanced sample across the 3 groups to support descriptive analysis for PK and safety at each dose schedule. Immunosuppressed participants will be prioritized to be enrolled into the new 600 mg IM dosing study group. This is in line with the indication for which the product is currently authorized for emergency use in the USA.

Specific changes of the sub-study CSP addendum are as follows:

Section 1.1 (Synopsis)

The sub-sections were updated to include the new 600 mg repeat dose participant study arm, extended study duration, and interim analyses. In addition the Cardiovascular Event Adjudication Committee was added to align with other AZD7442 studies.

Section 1.2 (Schematic)

The schematic has been updated to include the additional repeat dose participant arm and extended study duration.

Section 1.3 (Schedule of Activities)

A new Schedule of Activity table has been included for extended sub-study treatment and follow-up periods of the additional repeat dose participant groups. In addition the COVID-19 monitoring schedule for all groups were aligned.

Section 2.3.1 (Risk Assessment)

The table was updated to align with the current Investigator Brochure and SAE occurrence updated

Section 3 (Objectives and Endpoints)

The section has been updated to include the additional repeat dose participant arm.

Section 4.1 (Overall Study Design)

The section has been updated to include the additional repeat dose participant arm and extended study duration.

Section 4.2 (Scientific Rational for the Study Design)

The section has been updated to include the rational for the additional repeat dose participant arm and extended study duration.

Section 4.3 (Justification for Dose)

The section has been updated to include the justification of the 600 mg dose.

Section 6 (Study Intervention)

This section was edited to update status of the AZD7442 products.

Section 6.1 (IMPs Administered)

The section has been updated to include the additional repeat dose participant dose, extended study duration, and the new IMP dose used.

Section 6.2 (Preparation/Handling/Storage/Accountability)

The section has been updated to include new dose used.

Section 6.3 (Measure to Minimize Bias: Randomization and Blinding)

The section has been updated to include new dose used.

Section 6.5 (Concomitant Therapy)

Table 10 (Permitted, Restricted and Prohibited Medications) updated to align with other AZD7442 studies.

Section 8.1 (Efficacy Assessments)

The Section 8.1.1 (Monitoring COVID-19 Symptoms) has been updated to include the additional repeat dose participant arm schedule of activities for monitoring COVID-19 symptoms. In addition, language in Section 8.1.3 (Illness Visits) was added for clarification.

Section 8.4 (Overdose)

The section has been updated to include new dose used.

Section 8.5.2 (Immunogenicity Assessments)

Section 8.5.2.5 (Additional Serum Immunogenicity) updated to reflect what is in SoA. In addition serological assessments moved into Section 8.5.3 Pharmacodynamics.

Section 9.1 (Statistical Hypothesis)

The section has been updated to include new dose used.

Section 9.2 (Sample Size Determination)

Paragraph added to justify participant numbers chosen for the groups within this amendment.

9.4.2 (Secondary Endpoints)

Paragraph added to account for new COVID-19 treatments available.

Section 9.7 (Adjudication Committees)

This section was split into 2 sub-sections (Morbidity Adjudication Committee and newly added Cardiovascular Event Adjudication Committee) for 2 committees to align with other AZD7442 studies.

A5

Details on DSMB structure were

Various sections

Clarifications have been made where appropriate as well as other minor editorial and document formatting revisions **throughout**.

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1 PROTOCOL ADDENDUM SUMMARY

1.1 Synopsis

Sub-study Title: A Phase III, Multi-center, Open-label Sub-study in Adults to Assess the Safety, Pharmacokinetics (PK), and Immunogenicity of Repeat Doses of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061) (The PROVENT Repeat Dose Sub-study).

Rationale: AZD7442 is being evaluated for the prevention and treatment of Coronavirus Disease 2019 (COVID-19). PROVENT is an ongoing Phase III randomized, double-blind, placebo-controlled, multi-center study in adults to assess the safety and efficacy of a single dose of AZD7442 for pre-exposure prophylaxis of COVID-19 (PROVENT parent study). This PROVENT sub-study will assess the safety, PK, and immunogenicity of repeat doses of AZD7442 in participants currently enrolled in the PROVENT study who may benefit from a repeat dose of AZD7442. This sub-study will investigate whether additional doses of AZD7442 have an appropriate safety profile in this vulnerable population. Pharmacokinetic data will also be generated to evaluate whether repeat dosing can maintain serum concentrations of AZD7442 levels associated with protection against COVID-19.

Objectives and Endpoints:

Table 1 presents the objectives and endpoints for the repeat dose sub-study.

Table 1 Objectives and Endpoints for the Repeat Dose Sub-Study

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of repeat doses of AZD7442 300 and 600 mg IM	AEs, SAEs, MAAEs, and AESIs post repeat dose of IMP
Secondary	
To evaluate the PK of repeat doses of AZD7442 300 and 600 mg IM	Serum AZD7442 concentrations after repeat dosing PK parameters if data permit after repeat dosing
To evaluate ADA responses to repeat doses of AZD7442 300 and 600 mg IM in serum	Incidence of ADA to repeat doses of AZD7442 in serum
To determine anti-SARS-CoV-2 nAb levels in serum following repeat doses of AZD7442 300 and 600 mg IM	Post dose GMTs and GMFRs from baseline values after a repeat IM dose in SARS-CoV-2 nAbs (wild-type assay or pseudo-neutralization assay)

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; GMT, geometric mean titer; GMFR, geometric mean fold rise; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically attended adverse event; nAb, neutralizing antibody; PK, pharmacokinetic; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

For Exploratory objectives, see Section 3.

Overall Design:

This is a Phase III, multi-country, multi-center, open-label, sub-study assessing the safety, PK, and immunogenicity (ADA) of repeat doses of AZD7442. Participants at a subset of active PROVENT parent study sites in participating countries will be invited to enroll in this sub-study.

Participants will be adults who have been randomized and are actively participating in the PROVENT parent study and who may benefit from a repeat dose of AZD7442. There is no screening period in the sub-study and participants will retain their subject identification number from the parent study.

Participants will be eligible for inclusion in the sub-study once they have reached 12 ± 2 months post dose of IMP in the double-blind parent study. Eligible participants who have already completed their Day 366 Visit in the parent study will be unblinded, assigned to a sub-study group, and then undergo the sub-study Day 1 (SS-D1) assessments. For participants who have not yet completed their Day 366 Visit in the parent study, the SS-D1 visit will include the Day 366 assessments. Pre-dose Day 366 assessments will serve as baseline assessments for the sub-study.

All participants will receive AZD7442 in the repeat dose sub-study. Initially, participants will be assigned to one of two dosing interval groups, based on their double-blind IMP assignment in the parent study, as follows:

- Group 1 (~ 12-month repeat dose interval): Participants who received AZD7442 300 mg IM on Day 1 of the parent study will receive a second dose of AZD7442 300 mg IM on SS-D1.
- Group 2 (~ 6-month repeat dose interval): Participants who received placebo on Day 1 of the parent study will receive their first dose of AZD7442 300 mg IM on SS-D1 followed by a second dose on SS-D183.

At 6 months (SS-D183), a subset of participants from USA sites in Group 1 and Group 2 (evenly balanced between groups), who consent to receive additional AZD7442 600 mg doses approximately every 6 months will be assigned to a new arm - Group 3. All other participants will continue in the sub-study according to their originally assigned dosing interval group schedule. The addition of Group 3 will create 4 possible dosing cohorts, based on the how many doses of 300 mg AZD7442 received prior to entering Group 3 and whether or not this was followed by a further two doses of 600 mg AZD7442:

Group 1

- Cohort 1: AZD7442 300 mg, 300 mg

Group 2

- Cohort 2: Placebo, AZD7442 300 mg, 300 mg

Group 3

- Cohort 3 (from Group 1): AZD7442 300 mg, 30 0mg, 600 mg, 600 mg
- Cohort 4 (From Group 2): Placebo, AZD7442 300 mg, 600 mg, 600 mg

Group level recruitment caps may be placed to ensure 50 or more participants complete the study with their assigned dose and valid samples.

Group 1 and Group 2 will undergo safety follow-up for 456 days after the last dose of AZD7442, and Group 3 will undergo safety follow-up for 183 days after the last dose of AZD7442 (Figure 1).

Disclosure Statement: This is a safety/PK/immunogenicity study with three arms (all AZD7442 but with different doses, dosing intervals and/or study durations) that is not blinded.

Number of Participants: Approximately 500 participants will be enrolled from the parent PROVENT study into the sub-study and receive AZD7442. The aim is to approximately balance the proportion of participants derived from each of the AZD7442 and placebo arms from the double-blind parent study. If an imbalance between the arms is observed, a cap may be introduced.

To investigate repeat dosing with 600 mg IM, participants in the USA sites will be offered the option to be enrolled to receive repeat doses of 600 mg in Group 3 from SS-D183 onwards.

Intervention Groups and Duration: All participants will receive a repeat dose of AZD7442. The planned duration of the sub-study is 457 days for Group 1, 639 days for Group 2, and 548 days for Group 3.

Data Safety Monitoring Board: The independent DSMB monitoring the PROVENT parent study will provide safety oversight, to ensure safe and ethical conduct of the sub-study.

Statistical Methods

Primary Endpoint: The safety and tolerability of AZD7442 will primarily be assessed by the incidence of AEs, SAEs, MAAEs, and AESIs.

Interim analysis: An initial interim analysis is planned after a minimum of 50 participants at the first stage of enrollment of Group 1, who received AZD7442 on Day 1 of the parent PROVENT study have received a repeat dose of AZD7442 on SS-D1 and followed until SS-D29 (ie, for 28 days after their second dose of AZD7442). This interim analysis will assess the primary safety endpoint and available secondary endpoints. The first Data Review Meeting by

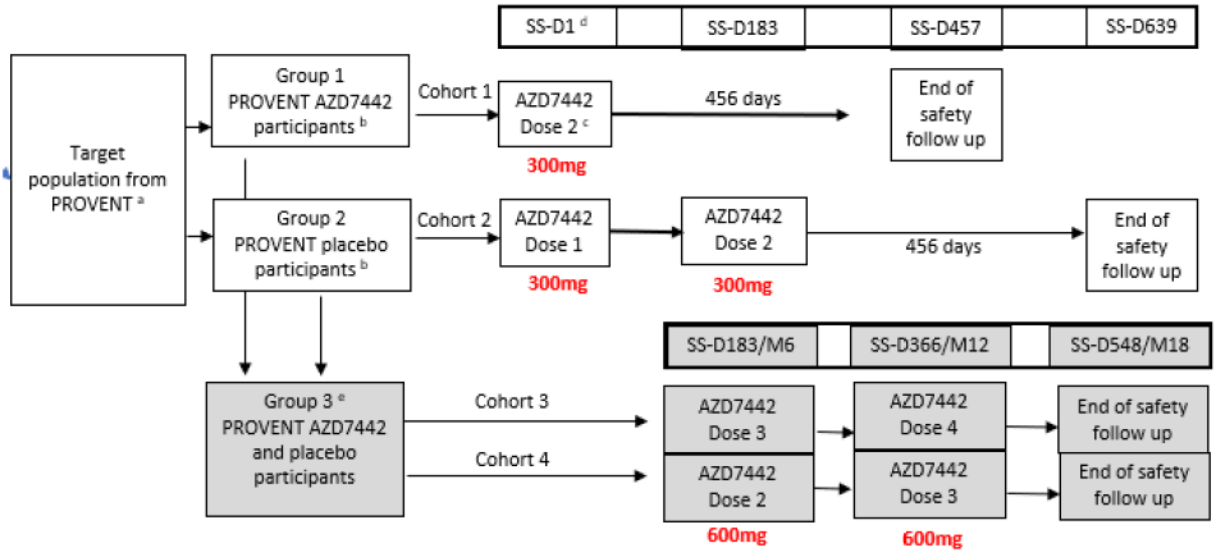
the DSMB will occur in conjunction with the interim analysis. Additional interim analyses may be conducted as required for any future regulatory commitments.

Morbidity Adjudication Committee: An independent Morbidity Adjudication Committee will assess blinded data to evaluate whether the causes of death for participants are considered COVID-19 associated.

Cardiovascular Event Adjudication Committee: An independent Cardiovascular Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of de-identified blinded data to systematically evaluate cardiovascular events.

1.2 Schematic

Figure 1 PROVENT Repeat Dose Sub-study Design



a Participants from PROVENT parent study who may benefit from a repeat dose of AZD7442.
b Based on randomization in the parent study.
c Participants will be eligible for the sub-study once they have reached 12 ± 2 months post dose in the double-blind parent study. Therefore, in the AZD7442 group, the dosing interval between Dose 1 (parent study) and Dose 2 (SS-D1) will be approximately 12 months.
d For participants who have not undergone a Day 366 visit in the parent study, the Day 366 assessments will be performed at SS-D1.
e Participants in Group 3 are those who consented to receive extended AZD7442 doses and comprise those from USA sites Group 1 and Group 2 (approximately evenly distributed between groups) who already received Dose 2 and Dose 1 of AZD7442 on SS-D1, respectively. Participants in Group 3 will now receive additional AZD7442 doses approximately every 6 months and will be followed for approximately 6 months after receiving their last dose at SS-D366.

M, month; SS-D, sub-study day.

1.3 Schedule of Activities

Table 2, Table 3, and Table 4 summarize the schedule of activities for the PROVENT repeat dose sub-study for Group 1 (participants randomized to AZD7442 in the parent study),

Group 2 (participants randomized to placebo in the parent study), and Group 3 (participants from Group 1 or Group 2 who will receive additional AZD74442 repeat doses) respectively. On dosing days, all assessments are to be obtained pre-dose unless otherwise specified. For participants who have not undergone a Day 366 visit in the parent study, the Day 366 assessments listed in the tables should be performed at SS-D1. For participants who have already undergone the Day 366 visit in the parent study, only the SS-D1 assessments need to be performed.

Participants who present with or report a COVID-19 qualifying symptom(s) after SS-D1 will be instructed to initiate Illness Visits and will be tested locally for SARS-CoV-2 (Table 5). If negative at Illness Visit Day 1, the participant will be instructed to stop Illness Visits and continue with the sub-study scheduled assessments in Table 2, Table 3, or Table 4. If positive, the participant will be instructed to continue with all Illness Visits and will have additional assessments per Table 5.

Table 2 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 1 (AZD7442 Participants from the PROVENT Parent Study)

Procedure	Parent study	Sub-study Treatment and Follow-up Period							Early Discontinuation Visit	For details, see Section:
Day[a]	**Day 366[b]**	**SS-D1[b]**	**SS-D29**	**SS-D92**	**SS-D183**	**SS-D275**	**SS-D366**	**SS-D457**		
Window (days)	**± 61**	**NA**	**± 3**	**± 5**	**± 10**	**± 15**	**± 15**	**± 15**		
Informed consent (sub-study)		X (pre-dose)								A 3
Verify eligibility criteria		X (pre-dose)								5.1, 5.2
Targeted physical examination	X	X	X	X	X	X	X		X	8.2.1
Weight		X								8.2.1
Vital signs (including pulse oximetry)	X (pre-dose)	X (post-dose[c])	X	X	X	X	X		X	8.2.2
Triplicate 12-lead ECG	X (pre-dose)		X		X		X		X	8.2.3
Serum chemistry	X (pre-dose)		X	X	X	X	X		X	8.2.4
Hematology	X (pre-dose)		X	X	X	X	X		X	8.2.4
Coagulation		X (pre-dose)	X	X	X	X	X		X	8.2.4
Urinalysis	X (pre-dose)		X	X	X	X	X		X	8.2.4
Cardiac biomarkers		X (pre-dose)	X		X		X		X	8.2.4
Troponin T/I		X (pre-dose)								8.2.4

Table 2 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 1 (AZD7442 Participants from the PROVENT Parent Study)

Procedure	**Parent study**	**Sub-study Treatment and Follow-up Period**							**Early Discontinuation Visit**	**For details, see Section:**
Day[a]	**Day 366[b]**	**SS-D1[b]**	**SS-D29**	**SS-D92**	**SS-D183**	**SS-D275**	**SS-D366**	**SS-D457**		
Window (days)	**± 61**	**NA**	**± 3**	**± 5**	**± 10**	**± 15**	**± 15**	**± 15**		
Pregnancy test – urine (WOCBP only)[d]	X (pre-dose)	X (pre-dose)	X	X	X	X	X		X	8.2.4.1
FSH (suspected postmenopausal women, < 50 years)[e]		X (pre-dose)								8.2.4.1
Concomitant medications	X		X	X	X	X	X		X	6.5
AZD7442 administration		Dose 2								6.1
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms and safety monitoring[f]	←	—	—	→						8.1.1, 8.3
Monthly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms and safety monitoring[f]					←	—	—	→		8.1.1, 8.3

Table 2 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 1 (AZD7442 Participants from the PROVENT Parent Study)

Procedure	Parent study	Sub-study Treatment and Follow-up Period							Early Discontinuation Visit	For details, see Section:
Day[a]	**Day 366**[b]	**SS-D1**[b]	**SS-D29**	**SS-D92**	**SS-D183**	**SS-D275**	**SS-D366**	**SS-D457**		
Window (days)	**± 61**	**NA**	**± 3**	**± 5**	**± 10**	**± 15**	**± 15**	**± 15**		
Documented SARS-CoV-2 RT-PCR test taken ≤ 3 days before SS-D1[g] OR Rapid SARS-CoV-2 antigen test (for screening criteria)		X (pre-dose)[h]								8.6.1.1
NP swab for SARS-CoV-2 RT-PCR (central laboratory)		X (pre-dose)[i]								8.6.1.1
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing[k]	X		X	X	X	X	X		X	8.5.2.2
Pharmacokinetics, pharmacodynamics, and ADA assessments										
Serum sample for AZD7442 pharmacokinetic assessment	X		X	X	X	X	X		X	8.5.1
Serum sample for AZD7442 ADA assessment	X		X	X	X	X	X		X	8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment	X		X	X	X	X	X		X	8.5.3.1

Table 2 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 1 (AZD7442 Participants from the PROVENT Parent Study)

Procedure	Parent study	Sub-study Treatment and Follow-up Period							Early Discontinuation Visit	For details, see Section:
Day[a]	**Day 366[b]**	**SS-D1[b]**	**SS-D29**	**SS-D92**	**SS-D183**	**SS-D275**	**SS-D366**	**SS-D457**		
Window (days)	**± 61**	**NA**	**± 3**	**± 5**	**± 10**	**± 15**	**± 15**	**± 15**		
Nasal adsorption for exploratory assessments[j]	X				X		X		X	8.5.2.3
Safety assessments										
Check injection sites[k]		X (post-dose)								8.2.5
AEs[l]	←	―	―	―	―	―	―	→	X	8.3
SAEs, MAAEs, and AESIs[f,l]	←	―	―	―	―	―	―	→	X	8.3
Other assessments										
Serum sample exploratory biomarkers	X		X	X	X	X	X		X	8.5.2.5

[a] To distinguish between sub-study visits and parent study visits the sub-study visits will be labeled as follows: the first sub-study visit Day 1 = SS-D1, sub-study visit Day 29 = SS-D29, and so on as applicable.

[b] For participants who have not undergone a Day 366 visit in the parent study, the Day 366 assessments listed above should be performed at SS-D1. For participants who have already undergone the Day 366 visit in the parent study, only the SS-D1 assessments need to be performed. Day 366 assessments in the parent study will be used as baseline in the sub-study.

[c] Perform 15 minutes (± 5 minutes) after both injections are complete.

[d] If the urine pregnancy test is positive or indeterminate, a quantitative serum β-hCG will be performed by the central laboratory for confirmation. On SS-D1, a negative pregnancy test is required before the participant receives IMP.

[e] FSH will be analyzed at SS-D1 to confirm postmenopausal status only in women < 50 years of age who have been amenorrhoeic for ≥ 12 months. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential. For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months' amenorrhea prior to SS-D1, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

[f] Weekly contact up to SS-D183 with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The Investigator will enquire about any COVID-19 symptoms from the past 7 days and other adverse events.
Monthly contact with participants from SS-D183 to EOS, to assess overall safety. The Investigator will ask about any COVID-19 qualifying symptoms and cardiac events from the past month and other AEs. Participants should be reminded to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms and to contact the site should they develop qualifying symptoms between each monthly contact.

[g] This test is not performed as part of the clinical study but must be available prior to enrollment.

[h] If a documented SARS-CoV-2 RT-PCR test is not available at screening, a rapid SARS-CoV-2 antigen test will be performed. Either test must be negative before dosing (see inclusion criteria in Section 5.1)

[i] Baseline sample, not a screening sample; results not needed prior to dosing.

[j] When test supplies are available, sampling should be performed.

[k] Perform immediately, 30 minutes (± 10 minutes) after both injections are complete, and prior to participant release (1 hour after IMP administration).

[l] After IMP administration, participants will be closely monitored for one hour before they can leave the site.

[m] AEs, SAEs, MAAEs, and AESIs will be assessed via a phone call at SS-D457.

On dosing days, all assessments are to be conducted pre-dose unless otherwise specified.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; IMP, investigational medicinal product; MAAE, medically attended adverse event; NA, not applicable; nAb, neutralizing antibody; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SS-D, sub-study day; WOCBP, women of childbearing potential.

Table 3 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 2 (Placebo Participants from PROVENT Parent Study)

Procedure	Parent Study	Sub-study Treatment and Follow-up Period										Early Discontinuation Visit	For details, see Section
Day[a]	Day 366[b]	SS-D1[b]	SS-D29	SS-D92	SS-D183	SS-D211	SS-D275	SS-D366	SS-D457	SS-D548	SS-D639		
Window (days)	± 61	NA	± 3	± 5	± 10	± 3	± 5	± 15	± 15	± 15	± 15		
Informed consent (sub-study)		X (pre-dose)											A 3
Verify eligibility criteria		X (pre-dose)											5.1, 5.2
Targeted physical examination	X	X	X	X	X (pre-dose)	X	X	X	X	X		X	8.2.1
Weight		X											8.2.1
Vital signs (including pulse oximetry)	X (pre-dose)	X (post-dose[c])	X	X	X (pre- and post-dose[c])	X	X	X	X	X		X	8.2.2
Triplicate 12-lead ECG	X (pre-dose)		X		X (pre-dose)	X		X		X		X	8.2.3
Serum chemistry	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.2.4
Hematology	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.2.4
Coagulation		X (pre-dose)	X	X	X (pre-dose)	X	X	X	X	X		X	8.2.4
Urinalysis	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.2.4

Table 3 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 2 (Placebo Participants from PROVENT Parent Study)

Procedure	Parent Study	Sub-study Treatment and Follow-up Period										Early Discontinuation Visit	For details, see Section
Day[a]	**Day 366[b]**	**SS-D1[b]**	**SS-D29**	**SS-D92**	**SS-D183**	**SS-D211**	**SS-D275**	**SS-D366**	**SS-D457**	**SS-D548**	**SS-D639**		
Window (days)	**± 61**	**NA**	**± 3**	**± 5**	**± 10**	**± 3**	**± 5**	**± 15**	**± 15**	**± 15**	**± 15**		
Cardiac biomarkers		X (pre-dose)	X		X (pre-dose)	X		X		X		X	8.2.4
Troponin T/I		X (pre-dose)											8.2.4
Pregnancy test – urine (WOCBP only)[d]		X (pre-dose)	X	X	X (pre-dose)	X	X	X	X	X		X	8.2.4.1
FSH (suspected postmenopausal women, < 50 years)[e]		X (pre-dose)											8.2.4.1
Concomitant medications	X		X	X	X	X	X	X		X		X	6.5
AZD7442 administration		Dose 1			Dose 2								6.1
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms and safety monitoring[f]	←	—	—	→									8.1.1, 8.3

Table 3 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 2 (Placebo Participants from PROVENT Parent Study)

Procedure	Parent Study	Sub-study Treatment and Follow-up Period										Early Discontinuation Visit	For details, see Section
Day[a]	Day 366[b]	SS-D1[b]	SS-D29	SS-D92	SS-D183	SS-D211	SS-D275	SS-D366	SS-D457	SS-D548	SS-D639		
Window (days)	± 61	NA	± 3	± 5	± 10	± 3	± 5	± 15	± 15	± 15	± 15		
Monthly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms and safety monitoring[f]					←	—	—	—	—	—	→		
Documented SARS-CoV-2 RT-PCR test taken ≤ 3 days before SS-D1[g] OR Rapid SARS-CoV-2 antigen test (for screening criteria)		X (pre-dose)[h]											8.6.1.1
NP swab for SARS-CoV-2 RT-PCR (central laboratory)		X (pre-dose)[i]											8.6.1.1
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing[k]	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.5.2.2

Table 3 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 2 (Placebo Participants from PROVENT Parent Study)

Procedure	Parent Study	Sub-study Treatment and Follow-up Period										Early Discontinuation Visit	For details, see Section
Day[a]	Day 366[b]	SS-D1[b]	SS-D29	SS-D92	SS-D183	SS-D211	SS-D275	SS-D366	SS-D457	SS-D548	SS-D639		
Window (days)	± 61	NA	± 3	± 5	± 10	± 3	± 5	± 15	± 15	± 15	± 15		
Pharmacokinetics, pharmacodynamics, and ADA assessments													
Serum sample for AZD7442 pharmacokinetic assessment	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.5.1
Serum sample for AZD7442 ADA assessment	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.5.3.1
Nasal adsorption for exploratory assessments[j]	X (pre-dose)				X (pre-dose)			X		X		X	8.5.2.3
Safety assessments													
Check injection sites[k]		X (post-dose)			X (post-dose)								8.2.5
AEs[l]	←	←	←	←	←	←	←	←	←	←	X[m]	X	8.3
SAEs, MAAEs, and AESIs[l]	←	←	←	←	←	←	←	←	←	←	X[m]	X	8.3

Table 3 Schedule of Activities: Sub-Study Treatment and Follow-up Period for Group 2 (Placebo Participants from PROVENT Parent Study)

Procedure	Parent Study	Sub-study Treatment and Follow-up Period										Early Discontinuation Visit	For details, see Section
Day[a]	Day 366[b]	SS-D1[b]	SS-D29	SS-D92	SS-D183	SS-D211	SS-D275	SS-D366	SS-D457	SS-D548	SS-D639		
Window (days)	± 61	NA	± 3	± 5	± 10	± 3	± 5	± 15	± 15	± 15	± 15		
Other assessments													
Serum sample exploratory biomarkers	X (pre-dose)		X	X	X (pre-dose)	X	X	X	X	X		X	8.5.2.5

[a] To distinguish between sub-study visits and parent study visits, the sub-study visits will be labeled as follows: the first sub-study visit Day 1 = SS-D1, sub-study visit Day 29 = SS-D29, and so on as applicable.

[b] For participants who have not undergone a Day 366 visit in the parent study, the Day 366 assessments listed above should be performed at SS-D1. For participants who have already undergone the Day 366 visit in the parent study, only the SS-D1 assessments need to be performed. Day 366 assessments in the parent study will be used as baseline in the sub-study.

[c] Perform 15 minutes (± 5 minutes) after both injections are complete.

[d] If the urine pregnancy test is positive or indeterminate, a quantitative serum β-hCG will be performed by the central laboratory for confirmation. At visits SS-D1 and SS-D183, a negative pregnancy test is required before the participant receives IMP.

[e] FSH will be analyzed at SS-D1 to confirm postmenopausal status only in women < 50 years of age who have been amenorrhoeic for ≥ 12 months. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential. For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months' amenorrhea prior to SS-D1, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

[f] Weekly contact up to SS-D183 with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The Investigator will enquire about any COVID-19 symptoms from the past 7 days and other adverse events.
Monthly contact with participants from SS-D183 to EOS, to assess overall safety. The Investigator will ask about any COVID-19 qualifying symptoms and cardiac events from the past month and other AEs. Participants should be reminded to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms and to contact the site should they develop qualifying symptoms between each monthly contact.

[g] This test is not performed as part of the clinical study but must be available prior to enrollment.

[h] If a documented SARS-CoV-2 RT-PCR test is not available at screening, a rapid SARS-CoV-2 antigen test will be performed. Either test must be negative before dosing (see inclusion criteria in Section 5.1)

[i] Baseline sample, not a screening sample; results not needed prior to dosing.

[j] When test supplies are available, sampling should be performed.

[k] Perform immediately, 30 minutes (± 10 minutes) after both injections are complete, and prior to participant release (1 hour after IMP administration).

[l] After IMP administration, participants will be closely monitored for one hour before they can leave the site.

[m] AEs, SAEs, MAARs, and AESIs will be assessed via a phone call at SS-D639.

The Day 366 Visit assessments in the parent study = baseline in the sub-study (ie, samples do not need to be collected twice).
On dosing days, all assessments are to be conducted pre-dose unless otherwise specified.
ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; IMP, investigational medicinal product; MAAE, medically attended adverse event; NA, not applicable; nAb, neutralizing antibody; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SS-D, sub-study day; WOCBP, women of childbearing potential.

Table 4 Schedule of Activities: Extended Sub-Study Treatment and Follow-up Period for Group 3 (AZD7442 and Placebo Participants from the PROVENT Parent Study)

Procedure	Sub-study Treatment and Follow-up Period							E/D Visit		For details, see Section
Month	**6**		**7**	**9**	**12**		**13**	**18**		
Day[a]	**SS-D183**	**SS-D190**	**SS-D211**	**SS-D275**	**SS-D366**	**SS-D373**	**SS-D394**	**SS-D548**		
Window	**± 10**		**± 3**	**± 5**	**± 10**		**± 3**	**± 15**		
Informed consent (reconsent)	X									A 3
Targeted physical examination	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.2.1
Vital signs (including pulse oximetry)	X[a] (pre- and post-dose)		X	X	X[a] (pre- and post-dose)		X	X	X	8.2.2
Triplicate 12-lead ECG	X (pre-dose)		X		X (pre-dose)		X	X	X	8.2.3
Serum chemistry	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.2.4
Hematology	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.2.4
Coagulation	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.2.4
Urinalysis	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.2.4
Cardiac biomarkers	X (pre-dose)		X		X (pre-dose)		X	X	X	8.2.4
Pregnancy test – urine (WOCBP only)[b]	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.2.4.1
Concomitant medications	X		X	X	X		X	X	X	6.5
AZD7442 administration	X				X					6.1
Virtual Safety Follow up one week post-AZD7442 administration[c]		X				X				
Monthly telephone/email/ text contacts - monitoring for COVID-19 qualifying symptoms and safety monitoring[d]	←							→		8.1.1, 8.3

Table 4 Schedule of Activities: Extended Sub-Study Treatment and Follow-up Period for Group 3 (AZD7442 and Placebo Participants from the PROVENT Parent Study)

Procedure	Sub-study Treatment and Follow-up Period							E/D Visit		For details, see Section
Month	**6**		**7**	**9**	**12**		**13**	**18**		
Day[a]	**SS-D183**	**SS-D190**	**SS-D211**	**SS-D275**	**SS-D366**	**SS-D373**	**SS-D394**	**SS-D548**		
Window	**± 10**		**± 3**	**± 5**	**± 10**		**± 3**	**± 15**		
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.5.2.2
Pharmacokinetics, pharmacodynamics, and ADA assessments										
Serum sample for AZD7442 pharmacokinetic assessment	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.5.1
Serum sample for AZD7442 ADA assessment	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.5.3.1
Nasal adsorption for exploratory assessments[e]	X (pre-dose)				X (pre-dose)			X	X	8.5.2.3
Safety assessments										
Check injection sites[f]	X (post-dose)				X (post-dose)					8.2.5
AEs, SAEs, MAAEs, and AESIs[g]	←							→	X	8.3
Other assessments										
Serum sample exploratory biomarkers	X (pre-dose)		X	X	X (pre-dose)		X	X	X	8.5.2.5

[a] Perform 15 minutes (± 5 minutes) after both injections are complete.

[b] If the urine pregnancy test is positive or indeterminate, a quantitative serum β-hCG will be performed by the central laboratory for confirmation. At visits SS-D183, SS-D366, and SS-D548, a negative pregnancy test is required before the participant receives IMP.

[c] AEs, SAEs, MAAEs, and AESIs, including injection site reactions, will be assessed via virtual phone call approximately one week after each dose.

[d] Monthly contact with participants to EOS to assess overall safety. The Investigator will ask about any COVID-19 qualifying symptoms and cardiac events from the past month and other AEs. Participants should be reminded to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms and to contact the site should they develop qualifying symptoms between each monthly contact.
[e] When test supplies are available, sampling should be performed.
[f] Perform immediately, 30 minutes (± 10 minutes) after both injections are complete, and prior to participant release (1 hour after IMP administration).
[g] After IMP administration, participants will be closely monitored for one hour before they can leave the site.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; COVID-19, coronavirus disease 2019; E/D, early discontinuation visit; ECG, electrocardiogram; EOS, end of study; IMP, investigational medicinal product; MAAE, medically attended adverse event; nAb, neutralizing antibody; SS-D, sub-study day; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; WOCBP, women of childbearing potential.

Table 5 Schedule of Activities: Illness Visits (Participants with Qualifying Clinical Symptoms)

Procedure [a]	**Site Visit**	**Home Collection by Participant**				**Site Visit for SARS-CoV-2 Positive Participants Only**[c]			**For details, see Section:**
Day[b]	**IL-D1**	**IL-D3**	**IL-D5**	**IL-D8**	**IL-D11**	**IL-D14**	**IL-D21**	**IL-D28**	
Window (days)	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Medical history	X					X	X	X	
Brief physical examination	X					X	X	X	8.2.1
Vital signs (including pulse oximetry)	X					X	X	X	8.2.2
Triplicate 12-lead ECG								X	8.2.3
Concomitant medication	←	—	—	—	—	—	—	→	6.5
Efficacy assessments									
Saliva sample for viral shedding[d]	X	X	X	X	X	X	X	X	8.6.1.2
Nasopharyngeal swab									
SARS-CoV-2 RT-PCR (local laboratory)[e]	X								8.6.1.1
SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel	X					X	X	X	8.6.1.1
Immunogenicity, Pharmacodynamics, and Pharmacokinetics									
PBMCs for B-cell and T-cell responses[e]	X					X			8.5.2.4
Serum sample for AZD7442 pharmacokinetic assessment	X					X	X	X	8.5.1
Serum sample for SARS-CoV-2 nAbs assessment	X					X	X	X	8.5.3.1

Table 5 Schedule of Activities: Illness Visits (Participants with Qualifying Clinical Symptoms)

Procedure [a]	**Site Visit**	**Home Collection by Participant**				**Site Visit for SARS-CoV-2 Positive Participants Only**[c]			**For details, see Section:**
Day[b]	**IL-D1**	**IL-D3**	**IL-D5**	**IL-D8**	**IL-D11**	**IL-D14**	**IL-D21**	**IL-D28**	
Window (days)	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Nasal adsorption for SARS-CoV-2 mucosal responses and exploratory assessments[f]	X					X		X	8.5.2.3
Serum sample for exploratory assessments	X					X	X	X	8.5.2.5
Safety assessments									
SAEs, MAAEs, and AESIs	←							→	8.3
Telephone contact for safety monitoring		X		X					
Coagulation	X					X	X	X	8.2.4

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive at ILD-1 will continue with the Illness Visits (ie, full visit series starting from IL-D1 and leading up to IL-D28), including any home collection requirements. Participants who test negative for SARS-CoV-2 at IL-D1 will be instructed to stop all Illness Visit assessments.

[b] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit Day 1 = 1IL-D1, Illness Visit Day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3, and so on as applicable.

[c] Where supported, home or mobile visits by study staff may substitute for site visits

[d] To be collected when operationally viable.

[e] A local test is required. If an immediate test result is not available, the participant should continue with the Illness Visit schedule until their result has been confirmed. Only if the local laboratory result is unavailable should the central laboratory result be used to assess continuation in Illness Visit schedule. In all instances both tests are required.

[f] When test supplies are available, sampling should be performed.

Note: The Illness Visit schedule is to be performed in addition to the scheduled visits in the main sub-study period (Table 2, Table 3, or Table 4). Where visits coincide, all assessments from the scheduled visit in Table 2, Table 3, or Table 4 and the Illness Visit should be performed.

AESI, adverse events of special interest; D, day; ECG, electrocardiogram; IL, illness visit; MAAE, medically attended adverse event; NA, not applicable; nAb, neutralizing antibody; PBMC, peripheral blood mononuclear cell; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

2 INTRODUCTION

See Section 2 of the PROVENT CSP for the parent study and the AZD7442 IB.

2.1 Study Rationale

AZD7442, a combination of 2 mAbs (AZD8895 and AZD1061), is being evaluated for the prevention or treatment of COVID-19. PROVENT is an ongoing Phase III, randomized, double-blind, placebo-controlled, multi-center study in adults to assess the safety and efficacy of a single dose of AZD7442 for pre-exposure prophylaxis of COVID-19 (PROVENT parent study). This PROVENT sub-study will assess the safety, PK, and immunogenicity of repeat doses of AZD7442 in participants currently enrolled in the PROVENT study who may benefit from a repeat dose of AZD7442. This study will investigate whether additional doses of AZD7442 have an appropriate safety profile in this vulnerable population. Pharmacokinetic data will also be generated to evaluate whether repeat dosing can maintain serum concentrations of AZD7442 associated with protection against COVID-19.

2.2 Background

See Section 2.2 of the PROVENT CSP for the parent study.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD7442 can be found in the AZD7442 IB.

2.3.1 Risk Assessment

Based on all available clinical study data with a cut-off date of 20 August 2021, there were no identified risks associated with AZD7442. The current risk assessment for AZD7442 is summarized in Table 6.

Table 6 Risk Assessment for AZD7442

Important Identified Risks	None
Identified Risks	None
Important Potential Risks	None
Potential Risks	Potential risks include injection-related reactions, ADE disease, serious hypersensitivity including anaphylaxis, and cardiac and thromboembolic events.
Reference Safety Information	For AZD7442, no SARs have been identified. Any SAE that is deemed to be related to the IP by the Investigator or the Sponsor will be treated as a suspected unexpected serious adverse reaction and appropriately expedited.

Based on a data cut-off of 20 August 2021.
ADE, antibody-dependent enhancement of disease; IP, investigational product; SAE, serious adverse event; SAR, serious adverse reaction.

In the PROVENT parent study, AZD7442 was generally well tolerated and preliminary analyses showed that overall AEs were balanced between the placebo and AZD7442 groups. A small number of cardiovascular serious adverse events (myocardial infarction and cardiac failure) have been reported in the PROVENT parent study at a higher rate in participants who received AZD7442 compared to placebo. All participants who experienced cardiac SAEs were at high risk for cardiac events, many of whom had a prior history of cardiovascular disease at baseline. There was no clear temporal pattern and a causal relationship between AZD7442 and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies. Monitoring of cardiovascular events will occur in this sub-study. There were no cases of severe COVID-19 or COVID-19-related deaths in those treated with AZD7442. In the placebo arm, there were 3 cases of severe COVID-19, which included 2 deaths.

In a separate Phase III AZD7442 study STORM CHASER (N = 1121), which enrolled a younger population with fewer baseline cardiac risk factors than PROVENT and no related cardiac SAEs at the time of primary analysis.

2.3.2 Benefit Assessment

The PROVENT primary analysis showed that AZD7442 achieved a statistically significant reduction in the incidence of symptomatic COVID-19, the study's primary endpoint. AZD7442 reduced the risk of developing symptomatic COVID-19 by 77% (95% CI: 46, 90), compared to placebo. The study accrued 25 cases of symptomatic COVID-19 at the primary analysis.

The participants included in this PROVENT sub-study are those most likely to benefit from repeat doses of AZD7442 for ongoing protection against COVID-19.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this sub-study, the potential risks identified in association with AZD7442 are justified by the anticipated benefits that may be afforded to participants at risk of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 7 lists the objectives and endpoints for the PROVENT repeat dose sub-study.

Table 7 Objectives and Endpoints for Repeat Dose Sub-Study

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of repeat doses of AZD7442 300 mg and 600 mg IM	AEs, SAEs, MAAEs, and AESIs post repeat dose of IMP
Secondary	
To evaluate the pharmacokinetics of repeat doses of AZD7442 300 mg and 600 mg IM	Serum AZD7442 concentrations following repeat dosing. PK parameters if data permit following repeat dosing
To evaluate ADA responses to repeat doses of AZD7442 300 mg and 600 mg IM in serum	Incidence of ADA to repeat doses of AZD7442 in serum
To determine anti-SARS-CoV-2 nAb levels in serum following repeat doses of AZD7442 300 mg and 600 mg IM	Post-treatment GMTs and GMFRs from baseline values after a repeat IM dose in SARS-CoV-2 nAbs (wild-type assay or pseudo-neutralization assay)
Exploratory	
PPD	PPD
PPD	PPD
PPD	PPD
PPD	PPD

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; GMT, geometric mean titers; GMFR, geometric mean fold rise; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically attended adverse event; nAb, neutralizing antibody; PK, pharmacokinetic; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase III, multi-country, multi-center, open-label, PROVENT sub-study assessing the safety, PK, and immunogenicity (ADA) of repeat doses of AZD7442. Participants at a subset

of active PROVENT parent study sites in participating countries will be invited to enroll in this sub-study.

Participants will be adults who have been randomized and are actively participating in the PROVENT parent study who may benefit from a repeat dose of AZD7442. The aim is to approximately balance the proportion of participants derived from each of the AZD7442 and placebo arms from the double-blind parent study. If an imbalance between the arms is observed, a cap may be introduced.

There is no screening period in the sub-study and participants will retain their subject identification number from the parent study.

Participants will be eligible for inclusion in the sub-study once they have reached 12 ± 2 months post dose of IMP in the double-blind parent study. Eligible participants who have already completed their Day 366 Visit in the parent study will be unblinded, assigned to a sub-study group, and then undergo the SS-D1 assessments. For participants who have not yet completed their Day 366 Visit in the parent study, the SS-D1 visit will include the Day 366 assessments. Pre-dose Day 366 assessments will serve as baseline assessments for the sub-study.

All participants will receive additional doses of AZD7442 in the repeat dose sub-study (Figure 1). Initially, participants will be assigned to one of two dosing interval groups as follows:

- Group 1 (~ 12-month repeat dose interval): Participants who received AZD7442 300 mg IM on Day 1 of the parent study will receive their second dose of AZD7442 300 mg IM on SS-D1.
- Group 2 (~ 6-month repeat dose interval): Participants who received placebo on Day 1 in the parent study will receive their first dose of AZD7442 300 mg IM on SS-D1 followed by a second dose on SS-D183.

At 6 months (SS-D183), a subset of participants from USA sites in Group 1 and Group 2 who consent to receive additional AZD7442 600 mg doses (approximately evenly distributed between groups) approximately every 6 months and will be assigned to a new arm - Group 3. All other participants will continue in the sub-study according to their originally assigned dosing interval group schedule. The addition of Group 3 will create 4 possible dosing cohorts, based on the how many doses of 300mg AZD7442 received prior to entering Group 3 and whether or not this was followed by a further two doses of 600mg AZD7442:

Group 1

- Cohort 1: AZD7442 300 mg, 300 mg

Group 2

- Cohort 2: Placebo, AZD7442 300mg, 300 mg

Group 3

- Cohort 3 (from Group 1): AZD7442 300 mg, 300 mg, 600 mg, 600 mg
- Cohort 4 (From Group 2): Placebo, AZD7442 300 mg, 600 mg, 600 mg

Group level recruitment caps may be placed to ensure 50 or more participants complete the study with their assigned dose and valid samples.

Group 1 and Group 2 will undergo safety follow-up for 456 days after the last dose of AZD7442, and Group 3 will undergo safety follow-up for 183 days after the last dose of AZD7442. The total duration of the sub-study will be 457 days for Group 1, 639 days for Group 2, and 548 days for Group 3.

4.2 Scientific Rationale for Study Design

This sub-study of the ongoing PROVENT parent study was designed to rapidly obtain clinical safety, PK, and immunogenicity data after repeat AZD7442 dosing in individuals who cannot receive a COVID-19 vaccine or are not expected to be adequately protected by a vaccine (ie, the target population for repeat dosing). This sub-study will aim to enrich the PROVENT study population with individuals who may benefit from a repeat dose of AZD7442 by targeting appropriate participant groups enrolled in the parent study (see Section 5.1).

The dosing intervals of approximately 6 months and 12 months to be evaluated in this study are based upon the extended half-life of AZD7442 and expected need for repeat dosing in clinical practice.

To generate repeat dose data as rapidly as possible, participants randomized to the PROVENT parent study who meet the sub-study inclusion criteria will be offered participation in the sub-study when it is initiated. This will result in some participants receiving a repeat dose as early as 10 months after the first dose in the parent study.

- Participants assigned to the 12-month dosing interval (Group 1) will be derived from the AZD7442 arm in the parent study. These participants will enter the sub-study and receive their second dose 12 ± 2 months after receiving their first dose in the parent study, (see Figure 1). An interim analysis will take place when a minimum of 50 participants have been followed until Day 29.
- Participants assigned to the 6-month dosing interval (Group 2) will be derived from the placebo arm in the parent study. This group will receive their first dose of AZD7442 upon entering the sub-study followed by a repeat dose at approximately 6 months (see

Figure 1). This group will generate data supporting assessment of a shorter repeat dosing time interval of the long-acting AZD7442 formulation.

- Participants assigned to the 18-month dosing schedule (Group 3) will be derived from a subset of participants at the USA sites in Group 1 and Group 2 in the sub-study (approximately evenly distributed between groups). This group will receive 2 doses of 600 mg IM AZD7442 at approximately 6 month intervals starting at SS-D183, following consent to the amended sub-study (see Figure 1), to align the dosing schedule per the FDA Fact sheet. This group will generate additional safety, PK, and immunogenicity data for longer-term repeat dosing time intervals of the long-acting AZD7442 formulation.

Evaluation of the safety, PK, and ADA immunogenicity of repeat dosing with AZD7442 will inform the following:

- Whether repeat dosing at different dosing intervals will maintain the serum concentrations of AZD7442 associated with protection against symptomatic disease in the parent study.
- Whether the safety profile and immunogenicity (ADA) profile after a repeat AZD7442 dose are comparable to the safety profile and immunogenicity profile observed after a single AZD7442 dose.

To provide safety data on AZD7442 for 5 half-lives, safety endpoints will be collected for 456 days after the last dose of IMP in Group 1 and Group 2.

4.3 Justification for Dose

The dose level, 300 mg IM, selected for this sub-study is based on the dose administered in the PROVENT parent study which demonstrated a favorable safety and efficacy profile in the primary analysis and is the proposed dose to be marketed (see Section 2.3). For further details on the dose justification, please refer to the AZD7442 IB.

The 600 mg IM dose selected for this sub-study extension is based on the 600 mg dose administered in the TACKLE study, and 600 mg AZD7442 is authorized for emergency use in the USA since 24 February 2022; both of which were considered generally safe and well-tolerated.

4.4 Justification for Study Population

In the PROVENT parent study, more than 75% of participants have co-morbidities, which includes those with a reduced immune response to vaccination. The primary analysis showed that AZD7442 was well tolerated, and AEs were balanced between the placebo and AZD7442 groups.

The PROVENT sub-study targets the study population most likely to benefit from receipt of a repeat dose of AZD7442. Participants will be eligible to enter the sub-study and the additional

Group 3, if they fulfill at least one of the following criteria: (a) immunocompromised and/or may be at increased risk for an inadequate response to a COVID-19 vaccination; (b), in the opinion of the Investigator, are at increased risk of severe COVID-19 (including participants who have not received a COVID-19 vaccine) (see Section 5.1).

4.5 End of Study Definition

A participant is considered to have completed the sub-study if they completed all phases of the study, including the last scheduled procedure shown in the SoA (see Section 1.3).

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

5 STUDY POPULATION

Planned protocol deviations are not considered acceptable. A protocol deviation that is suspected or known to have the potential to significantly impact a participant's safety, physical or mental integrity, or scientific value will be classified as a serious breach.

5.1 Inclusion Criteria

Participants are eligible to be included in the sub-study if all the following criteria apply:

1 The participant has been randomized, dosed, and is ongoing in the PROVENT parent study and is 12 ± 2 months post first dose of blinded IMP.

2 If one or more of the following apply:

(a) Immunocompromised and/or may be at increased risk for an inadequate immune response to a COVID-19 vaccine, including:

- Elderly, ie, ≥ 60 years old
- Obese, ie, Body Mass Index≥ 30
- Congestive heart failure
- Chronic lung disease
- Chronic kidney disease, ie, GFR < 30 mL/min/1.73 m^2 (Lamb et al 2013)
- Chronic liver disease
- Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, human immunodeficiency virus, use of corticosteroids, or use of other immunosuppressive medicines
- Intolerant of vaccine. Defined as previous history of severe AE or SAE after receiving any approved vaccine.

(b) In the opinion of the Investigator, are at increased risk and would benefit from a repeat dose of AZD7442 (eg, participants who have a chronic condition that increases

their risk of severe COVID-19 or those who have not been vaccinated against COVID-19).

3 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the one month prior to enrollment to the sub-study, with no acute change in condition at the time of sub-study enrollment as judged by the Investigator. This includes conditions newly diagnosed since the participant entered the parent study.

4 Documented negative SARS-CoV-2 RT-PCR test collected ≤ 3 days prior to SS-D1 or a negative rapid SARS-CoV-2 antigen test at screening.

Reproduction

5 Contraceptive use by men or women:

(a) Male Participants: Contraception for male participants is not required, however, to avoid the transfer of any fluids, all male participants must use a condom from SS-D1 and agree to continue through 365 days following administration of the IMP.

(b) Female Participants:

- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women 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:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Women 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 SS-D1 and agree to continue through 365 days following administration of the IMP. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

All women of childbearing potential must have a negative urine pregnancy test result before dosing at Visit SS-D1 and at SS-D183 as indicated in the SoA (see Section 1.3).

Examples of highly effective birth control methods are listed in Table 8.

Table 8 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	• Combined (estrogen- and progestogen-containing hormonal contraception) associated with inhibition of ovulation ° Oral (combined pill) ° Intravaginal ° Injectable ° Transdermal (patch) • Progestogen-only hormonal contraception associated with inhibition of ovulation ° Oral ° Injectable ° Implantable

[a] This is also considered a hormonal method.
[b] Provided the partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant.

5.2 Exclusion Criteria

Participants are to be excluded from the study if any of the following criteria apply:

1 Have received a COVID-19 vaccination ≤ 14 days before SS-D1 or plan to receive a COVID-19 vaccination ≤ 14 days after SS-D1. (Such participants can subsequently be included in the study once they have reached > 14 days after their last dose of vaccine).

2 Have 2 or more untreated cardiac risk factors or suspected unstable cardiac disease.

3 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

5.3 Lifestyle Considerations

Lifestyle considerations for the sub-study are consistent with those in the parent study. See Section 5.3 in the PROVENT CSP for details.

5.4 Screen Failures

Not applicable. See Section 5.2 for guidance on COVID-19 vaccinations.

6 STUDY INTERVENTION

The IMP is defined as any investigational intervention(s) or authorized product(s) intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

6.1 IMP(s) Administered

6.1.1 IMP

The majority of participants will receive at least one dose of 300 mg dose of AZD7442 (divided in 2 sequential injections, one for each mAb component) administered IM (Table 9). Participants who were randomized to AZD7442 in the parent study (Group 1) received their first dose of AZD7442 on Day 1 of the parent study and will receive their second dose on SS-D1 in the sub-study. Participants who were randomized to placebo in the parent study (Group 2) will receive their first and second AZD7442 doses on SS-D1 and SS-D183 of the sub-study, respectively.

Participants consenting to the sub-study extension amendment (Group 3) will receive 2 repeat doses of 600 mg IM AZD7442 at 6 month intervals.

A 300 mg and 600 mg dose of AZD7442 consists of 2 IM injections (one in each gluteal region). If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection in the sub-study, but before the subsequent IM injections, further IMP should not be given. For details on the treatment of anaphylactic reactions after IMP IM injections see Appendix E. For further details on IMP discontinuation, see Section 7.1.

Table 9 Investigational Product

Intervention name	300 mg AZD7442 (AZD8895 + AZD1061)	600 mg AZD7442 (AZD8895 + AZD1061)
Dose formulation	**Liquid Product** AZD7442 will be supplied as separate vials of AZD8895 and AZD1061 as 150 mg colorless to slightly yellow, clear to opalescent solutions for injection. The solutions contain 100 mg/mL of active ingredient (AZD8895 or AZD1061) in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. The label-claim volume is 1.5 mL.	**Liquid Product** AZD7442 will be supplied as separate vials of AZD8895 and AZD1061 as 300 mg colorless to slightly yellow, clear to opalescent solutions for injection. The solutions contain 100 mg/mL of active ingredient (AZD8895 or AZD1061) in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. The label-claim volume is 3.0 mL.
Unit dose strength(s)	300 mg AZD7442 consisting of 150 mg each of AZD8895 and AZD1061 at 100 mg/mL	600 mg AZD7442 consisting of 300 mg AZD8895 and 300 mg AZD1061 each at 100 mg/mL
Dosage level(s)	300 mg single dose of AZD7442 (150 mg of AZD8895 and 150 mg of AZD1061)	600 mg single dose of AZD7442 (300 mg of AZD8895 and 300 mg of AZD1061)
Route of administration	Two IM injections of 1.5 mL each (one in each gluteal region)	Two IM injections of 3 mL each (one in each gluteal region)
Use	Experimental	Experimental
Sourcing	AZD7442 (AZD8895 + AZD1061): AstraZeneca.	AZD7442 (AZD8895 + AZD1061): AstraZeneca
Packaging and labeling	IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement.	IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement.

IM, intramuscular; IMP, investigational medicinal product; w/v, weight per volume.

6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received, and any discrepancies are reported and resolved before use of the IMP.
- Only participants enrolled in the sub-study may receive IMP and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused IMPs are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration Instructions

Each vial selected for dose preparation should be inspected. If there are any defects noted with the IMP, the Investigator and site monitor should be notified immediately.

6.2.1.1 Investigational Product Inspection

AZD7442 IMP is comprised of 2 separate drug products, AZD8895 and AZD1061, to be administered sequentially. One kit is required for the 300 mg dose and 2 kits are required for the 600 mg dose.

Drug Product

The AZD8895 and AZD1061 DPs are each supplied as sterile clear to opalescent, colorless to slightly yellow solutions, with a label-claim of 150 mg at 100 mg/mL per vial.

6.2.1.2 Dose Calculation

For AZD7442 (AZD8895 and AZD1061), the doses will be prepared directly from the AZD8895 and AZD1061 DP vials. AZD8895 and AZD1061 will be administered individually, using separate components.

6.2.1.3 Dose Preparation Steps

The 2 DPs AZD8895 and AZD1061 (comprising AZD7442), must both be administered separately to the participant in sequential order, with no participant receiving doses of AZD8895 without also receiving the matching dose of AZD1061. The dose of AZD8895 must be administered first. The dose of AZD8895 and AZD1061 for administration must be prepared by the IMP Manager or other qualified professional using aseptic technique, and who should only remove the required DP vials for participant dosing from storage. No incompatibilities have been observed between AZD7442 and disposable polypropylene or polycarbonate syringes used for IM administration.

Dose Preparation and Administration for AZD7442 (AZD8895/AZD1061)

The dose of AZD7442 (AZD8895 and AZD1061) for administration must be prepared by the Investigator's or site's designated IMP Manager using aseptic technique. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2 °C to 8 °C (36 °F to 46 °F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials. Each AZD8895

and AZD1061 vial must be used only once to prepare a single dose. AZD7442 (AZD8895 and AZD1061) does not contain preservatives, and any unused portion must be discarded.

A separate disposable syringe with a 22 to 25 gauge and 1 to 1.5 in (25 to 38 mm) length needle should be used for each AZD8895 and AZD1061 DP injection. Each DP should be administered as a separate single injection and administered sequentially. Intramuscular doses should be prepared by accurately withdrawing 1.5 mL volume of DP for Group 1 and Group 2 and 3.0 mL of DP for Group 3 into an appropriately sized latex-free disposable polypropylene or polycarbonate syringe. AZD8895 and AZD1061 should be administered according to standard practice procedures for IM injections, with one injection in each gluteal region. The IMP does not contain preservatives and any unused portion must be discarded.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study in which all participants receive AZD7442 300 mg followed by either a 300 mg or 600 mg IM dose(s). Where a participant does not meet all the eligibility criteria but incorrectly received IMP, the Investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the Investigator regarding whether to continue or discontinue the participant.

6.4 IMP Compliance

Dosing will take place under the guidance of study personnel, may occur at study sites, mobile units, or within long-term care facilities, and will be recorded in the eCRF.

Long-term care facilities include: skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults.

Compliance will be assured by direct supervision and witnessing of the IMP administration. If a problem occurs during dosing, such as needle break, no redosing is permitted.

6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines, over-the-counter, or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the 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 10 lists the permitted, restricted, and prohibited medications during the sub-study.

Table 10 Permitted, Restricted, and Prohibited Medications

Use Category	Type of medication/treatment	Timeline/instructions
Permitted	Routine Vaccines	Licensed influenza vaccines are permitted at any time. All other routine vaccines are permitted provided the routine vaccine is received > 30 days prior to, or following an IMP dose.
	COVID-19 Vaccines	Vaccines for the prevention of SARS-CoV-2 or COVID-19 are permitted provided the vaccine is received ≥ 14 days prior to IMP administration or following receipt of IMP administration (see Section 6.5.1).
	Allergen immunotherapy	Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Visit 1 in the parent study and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as IMP. 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, provided the participant is stable on maintenance dose (at steady state) prior to Visit 1 in the parent study. • Receipt of approved/licensed treatments for the prevention of COVID-19 are permitted during the follow-up period (starting ≥ 3 months after the last dose of AZD7442) as per local guidelines/standard of care and should be documented as concomitant medication. ° **Treatment of COVID-19 with other monoclonal antibodies will require that the participant not receive any further AZD7442 doses as part of the study, but should remain in study for long-term safety follow-up.**

Table 10 Permitted, Restricted, and Prohibited Medications

Use Category	Type of medication/treatment	Timeline/instructions
	Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers or, where appropriate, Investigators should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving IMP should be treated according to local standard of care, including investigational agents outside a clinical trial setting.	
Restricted	• Products indicated for the prevention of SARS-CoV-2 or COVID-19 (including those under investigation or authorized under early access provisions) • Hydroxychloroquine • Chloroquine • Ivermectin • HIV protease inhibitors • Convalescent COVID-19 plasma and sera • Hyperimmune globulin	• Note: For participants who develop SARS-CoV-2 infection or become hospitalized with COVID-19, receipt of approved/licensed treatment options are permitted and participants should be treated according to local standard of care, including investigational agents under Emergency Use Authorization or equivalent regulations. • Use of hydroxychloroquine is acceptable if used chronically for autoimmune disease, and the dose is stable prior to Day 1 and up to Day 29. • Use of chloroquine if used to treat a parasitic infection • Use of ivermectin is acceptable if used to treat a parasitic infection • HIV protease inhibitors are acceptable if used chronically for HIV infection, and the dose is stable prior to Day 1 and up to Day 29.
	Contraceptive methods	See Section 5.1 in the parent study protocol.
	Blood/plasma donation	Participants must abstain from donating blood or plasma from the time of informed consent and for 5 half-lives after dose of study drug; ie, one year.

COVID-19, coronavirus disease 2019; HIV, Human immunodeficiency virus; IMP, investigational medicinal product; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

6.5.1 COVID-19 Vaccines

Participants who have received a previous dose or doses of a COVID-19 vaccine are permitted to be included in the sub-study; however, participants enrolling in the repeat dose sub-study must not have received a dose of a COVID-19 vaccine ≤ 14 days before receiving a dose of IMP or plan to receive a COVID-19 vaccination ≤ 14 days after receiving a dose of IMP. Such participants can subsequently be included in the sub-study once they have reached > 14 days after the last dose of vaccine. Otherwise, participants can elect to receive a COVID-19 vaccination at any time during the sub-study.

6.6 Dose Modification

The IMP will be administered as described in Section 6.1.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see definition in Section 4.5).

7 DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study IMP

It may be necessary for a participant to permanently discontinue (definitive discontinuation) IMP. If IMP is permanently discontinued, the participant should remain in the study to be evaluated. See the SoA (see Section 1.3) for data to be collected at the time of discontinuation of IMP and follow-up, and for any further evaluations that need to be completed.

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

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

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the sub-study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted, as shown in the SoA (see Section 1.3). 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.
- 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 at the time of withdrawal. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed

consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Once a participant has been document as lost to follow-up, they cannot rejoin the study.

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

- The study 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, including those who did not receive IMP. 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.

7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- Any death, SAE, or other safety finding assessed as related to IMP that, in the opinion of the Sponsor, may preclude further administration of IMP.

- If one or more participant experiences a grade IV hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If 2 or more participants, within the first 50 participants experience a grade III or higher hypersensitivity reaction.
- If 2 or more participants, within the first 50 participants receiving the second dose experience a grade III or higher injection site reaction.

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 IMP.
- 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 timeframe defined in the SoA.

8.1 Efficacy Assessments

This primary objective of this sub-study is safety and tolerability. Efficacy assessments described in this section are exploratory.

8.1.1 Monitoring COVID-19 Symptoms

To determine the incidence of infection, study sites will contact participants weekly (telephone/email/text) through to the SS-D183 and then monthly to the end of the study, with reminders to monitor for COVID-19 symptoms and cardiac events. During these contacts the Investigator will enquire about any COVID-19 symptoms (see Table 11) and cardiac events from the past 7 days or month respectively and will need to initiate Illness Visits within 3 days if such symptoms are reported. Participants who present with at least one of the COVID-19 qualifying symptoms listed in Table 11, must contact the study site.

Participants who present with a COVID-19 qualifying symptom(s) after SS-D1 will be instructed to initiate Illness Visits and will be tested locally for SARS-CoV-2 (see Section 8.6.1.1). If negative at Illness Visit D1, the participant will be instructed to stop Illness Visits and continue with the with the sub-study scheduled assessments (ie, Table 2, Table 3, or Table 4). If positive, the participant will be instructed to continue to complete all Illness Visits and will have additional assessments per Table 5. COVID-19 qualifying symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as an AE.

Table 11 COVID-19 Qualifying Symptoms

Participant must present with at least one of the following symptoms:	
Duration	**Symptom**
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
	New onset confusion (only for participants ≥ 60 yo)
	Appetite loss or decrease food intake (only for participants ≥ 60 yo)
	Increased supplemental oxygen requirement (only for participants ≥ 60 yo on baseline supplemental oxygen)
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhea

Adapted from CDC 2021
CDC, Centers for Disease Control and Prevention; yo, years old.

8.1.2 Severe or Critical Criteria

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia (oxygen saturation < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Table 12). Confirmed positive cases of COVID-19 must have a WHO Clinical Progression score recorded in the eCRF.

Table 12 WHO Clinical Progression Scale

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

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; NIV, non-invasive ventilation; RNA, ribonucleic acid; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation.
Marshall et al 2020.

8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.1) will be instructed to visit the study site for initiation of illness assessments (Table 5); where supported, home or mobile visits may be substituted for the site visits. Symptomatic participants will complete the IL-D1 and will be instructed to continue with the home collection requirements. Results of SARS-CoV-2 RT-PCR test will be available during the home collection period and participants will be informed of their status. The results of the COVID-19 RT-PCR testing should also be reported to the participants' primary care providers. Symptomatic participants will continue with the Illness Visits until a laboratory result is available. Only participants who test positive by the local laboratory results (or central laboratory results, if local not available) will be instructed to

continue with the Illness Visits and complete the entire Illness Visit series, including home collection requirements. All home lab kits should be brought to all subsequent Illness Visits. Participants who test negative for SARS-CoV-2 at IL-D1 will be instructed to stop all Illness Visit assessments and return the home lab kits. Participants will continue with follow-up visits per Table 2 or Table 3 or Table 4.

The Illness Visit schedule is to be performed in addition to the scheduled visit in Table 2, Table 3 or Table 4. Where visits coincide, all assessments from the scheduled visit and Illness Visit should be performed.

To distinguish between the scheduled visits for the treatment and follow-up period (Table 2, Table 3 or Table 4) and the Illness Visits (Table 5), and to distinguish between illness episodes the visits will be labeled as follows: for the first episode Illness Visit Day 1 = 1IL-D1, Illness Visit Day 3 = 1IL-D3 etc, and for the second episode 2IL-D1, 2IL-D3, and so on as applicable.

8.1.4 SARS-CoV-2 Testing and Other Virology Assessments

At the IL-D1, NP swabs will be collected for local and central laboratories and tested for SARS-CoV-2 by authorized RT-PCR assays (see Section 8.6.1.1).

Resistance monitoring as performed by genotypic and phenotypic characterization of virus isolated from Illness Visits may be conducted per the SoA (see Section 1.3 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out at time points per the SoA, and as outlined in Section 8.6.1.1.

Saliva may be collected during site Illness Visits and by self-collection at home throughout the Illness Visits to quantify duration of viral shedding (see Section 8.6.1.2).

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

Targeted physical examinations will be performed as specified in the SoA (see Section 1.3).

- A targeted physical examination will include areas suggested by changes to the medical history, vulnerable medical conditions, and reported clinical complaints during the study visit. Each clinically significant abnormal finding following vaccination will be recorded as an AE.
- Weight will be recorded at the first sub-study visit.

All physical examinations will be performed by a licensed healthcare provider including, but not limited to, physician, physician assistant, or licensed nurse practitioner.

8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the SoA (see Section 1.3). The participant should be resting prior to the collection of vital signs.

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

8.2.3 Electrocardiograms

Triplicate 12-lead ECGs will be performed at time points specified in the SoA (see Section 1.3). A 12-lead safety ECG will be obtained after 5 minutes' supine rest, using the sites own ECG machines.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, urinalysis, and cardiac biomarkers will be taken at the visits indicated in the SoA (see Section 1.3).

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 clinical chemistry, hematology, coagulation, urinalysis, cardiac/thrombosis biomarkers, serum β-hCG, and FSH will be performed at a central laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Instruction for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

The following laboratory variables will be measured.

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)	Reticulocytes absolute count
Serum Clinical 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
Calcium	Conjugated bilirubin
Phosphate	Creatine Kinase
Glucose	
C-reactive protein (CRP)	
Urinalysis	
Glucose	Blood
Protein	Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)
Coagulation	
International normalized ratio (INR)	Prothrombin Time (PT)
Activated partial thrombin time (aPTT)	

Note: In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix D. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

Cardiac/Thrombosis Biomarkers	
D-dimer	Serum-LDL cholesterol
P-selectin	Serum-HDL cholesterol
Thrombin	hs-CRP[a]
Factor VIII levels	
Total serum cholesterol	Troponin T/I[b]

[a] High-sensitivity C-reactive protein (hs-CRP)
[b] Only to be collected on sub-study Day 1.

8.2.4.1 Females Only

Pregnancy test (women of childbearing potential only)	
Urine human beta chorionic gonadotrophin (β-hCG) (pre-dose)	Serum β-hCG[a]
Suspected postmenopausal women < 50 years only)	
Follicle-stimulating hormone (FSH)[b]	

[a] If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.
[b] FSH will be analyzed at the screening visit to confirm postmenopausal status only in women < 50 years of age who have been amenorrhoeic for ≥ 12 months. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential. For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months' amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

8.2.5 Injection Site Inspection

An injection site inspection will be performed after administration of IMP according to Table 13 (see Section 1.3).

Table 13 Injection Site Inspection

Procedure/Time after both injections have been administered	Immediately after IMP administration	30 minutes (± 10 minutes)	Immediately prior to participant release
Visual inspection of site	X	X	X
Palpation of site	X	X	X
Participant will be asked			
Are you experiencing any discomfort?	X	X	X
If yes, has the feeling of discomfort changed since you received the injection		X	X

IMP, investigational medicinal product

Any AEs should be reported as described in Section 8.3.

8.2.5.1 Monitoring After IMP Administration

In addition to the injection site inspection, safety monitoring will be performed after IMP administration. Participants will be closely monitored for one hour post IMP administration.

8.3 Adverse Events and Serious Adverse Events

The 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

All AEs and SAEs will be collected from the time of IMP administration throughout the study, up to and including the last visit.

Serious adverse events will be recorded from the time of signing of the sub-study ICF.

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

8.3.2 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. Medical records associated with SAEs should be collected and redacted copies provided to the CRO/Sponsor, when requested.

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 IMP(s) (yes or no)
- Action taken with regard to IMP
- If the AE caused participant's withdrawal from the 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
- Cause of death related to COVID-19 (yes/no/unknown)
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

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.

It is important to distinguish between serious and severe AEs:

- Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B 2.
- An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

8.3.3 Causality Collection

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

For SAEs, causal relationship should also be assessed for other medication(s) and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

8.3.4 Adverse Events of Special Interest

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

Adverse events of special interest are events of scientific and medical interest, specific to the further understanding of the IMP safety profile, and require close monitoring and rapid communication by the Investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.9. See also the AZD7442 IB, for additional information on AESIs.

AESIs for AZD7442 are listed below. They include:

- Anaphylaxis and other serious hypersensitivity reactions (Appendix E).
- Injection site reactions.
- Cardiac ischemia, cardiac failure, and thrombotic events.

8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoA (see Section 1.3).

Medically attended adverse events are defined as AEs leading to medically attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. Adverse events, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits will not be considered MAAEs.

8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider, or reported in response to the open question from the study site staff: 'Have you 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. Symptoms of COVID-19, confirmed SARS-CoV-2 infection, and/or diagnosis of COVID-19 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 protocol-mandated laboratory tests, vital signs, ECG, and other safety assessments will be summarized in the CSR.

Deterioration, as compared to baseline in protocol-mandated safety assessments, should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the IMP, 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 IMP, eg, dose adjustment or drug interruption).

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

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

8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN, together with TBL $\geq 2 \times$ ULN *and* confirmed as a HL case should be reported as an SAE.

AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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 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 have to be reported, whether or not considered causally related to the IMP or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

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

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

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative via paper form to a global safety mailbox.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed. For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

8.3.10.1 Maternal Exposure

The IMP should not be given to pregnant women.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital

abnormalities/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 abnormality) 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 **one 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 one 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.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child during the study and for 365 days following each dose of AZD7442.

In case of pregnancy of the partner of a male participant, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should, if possible, be obtained and documented.

Please refer to Section 8.3.10 for further details.

8.3.11 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs 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 works with the Investigator to ensure that all relevant information is completed within **one** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar day(s)** if there is

an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of AZD7442 > 150 mg of either individual mAb for the 300 mg dose or >300 mg of either individual mAb for the 600 mg dose or an additional dose given by mistake outside the study schedule will be considered an overdose.

AstraZeneca does not recommend a specific treatment for an overdose. Symptoms of overdose should be treated as per clinical judgment.

- 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 of an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, and within 30 days for other overdoses.

8.5 Human Biological Samples

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

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

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further

evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes, but is not limited to, further characterization of any ADAs, confirmation and/or requalification of the assay, as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics Assessments

- Serum samples will be collected for measurement of serum concentrations of AZD7442 (AZD8895 and AZD1061), as specified in Table 2, Table 3, and Table 4.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons.
- Samples collected for analyses of AZD7442 serum concentration may be used to evaluate safety or efficacy aspects.
- Samples will be collected, labeled, stored, and shipped, as detailed in the Laboratory Manual.
- Serum AZD8895 and AZD1061 concentrations will be summarized descriptively by time point and PK parameters (eg, AUC, $t_{1/2}$) will be derived if data allow. The AZD8895 and AZD1061 data will be further analyzed with population PK methods to characterize the multiple dose PK for different dosing intervals.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred Sample Reanalysis (ISR), if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Serum samples for ADA immunogenicity assessments will be collected according to Table 2, Table 3, or Table 4. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.5.2.1 Antidrug Antibody Assessments

Serum samples for determination of ADA will be conducted on behalf of AstraZeneca, using a validated assay. Serum samples for determination of ADAs will be collected as specified in the SoA (see Section 1.3). Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination.

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the SoA (see Section 1.3). Baseline serostatus and the rate of SARS-CoV-2 infection in participants in this sub-study will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 N assay operated by an authorized laboratory.

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8.5.3 Pharmacodynamics

8.5.3.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (see Section 1.3). Authorized laboratories may measure nAbs to SARS-CoV-2 using validated live virus neutralization assays or pseudo-neutralization assays.

Serologic assessment to seasonal coronavirus antigens may also be assessed quantitatively using a qualified multiplexed meso scale discovery (MSD) immunoassay. Exploratory sera samples may be utilized to investigate additional humoral and cellular immune responses, as well as potential correlates of protection as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

8.6 Human Biological Sample for Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

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

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. Saliva samples may be collected at site Illness Visits and by the participants during the home collection period. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between pharmacodynamics and ADA immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

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

8.6.1.1 Virologic Assessments

Participants who have not received a negative SARS-CoV-2 RT-PCR test result ≤ 3 days before study entry will require a negative result from a SARS-CoV-2 rapid antigen test on SS-D1 to be included into the sub-study.

Nasopharyngeal swabs will also be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by the central laboratories according to the time points specified in the SoA (Section 1.3). Instructions for obtaining and processing NP swab samples are provided in the Laboratory Manual. The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing (NGS) at IL-D1, IL-D14, IL-D21, and IL-D28. Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR. Amino acid changes identified by genotypic analyses of the

S trimer protein ectodomain (AA 20-1213) can be evaluated by either a spike trimer binding affinity assay and/or a recombinant SARS-CoV-2 Spike-pseudovirus neutralization assay. Additional details on clinical virology analyses, including molecular surveillance of the S protein in global circulation will be provided in the Virology Analysis Plan.

Local and central assessments should be collected per the schedule of activities; where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in NP swabs in a central laboratory operated on behalf of the Sponsor at IL-D1.

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8.7 Optional Genomics Initiative Sample

Genomics sampling is not applicable in this sub-study.

8.8 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not applicable in this sub-study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective of this sub-study is to assess the safety and tolerability of repeat doses of AZD7442 300 mg and 600 mg IM. No hypotheses will be tested.

9.2 Sample Size Determination

Approximately 500 participants will be enrolled in the sub-study to receive repeat doses of AZD7442. If the true adverse event rate is 1%, the probability of observing at least one AE in

500 participants is > 99%. The incidence of 1% is the lower limit of the category of common AEs (between infrequent and frequent AEs) by the Council for International Organizations of Medical Sciences (CIOMS) Working Group (CIOMS 1999).

Participants in the sub-study will received repeat dosing of AZD7442 as outlined in Figure 1. Group level recruitment caps may be placed to ensure at least 50 subjects complete the study with their assigned dose and valid samples for analysis. A study sample of 50 or more participants will have greater than a 90% probability to estimate a 95% confidence interval within 60% to 140% of the assumed true geometric mean for pharmacokinetic parameters. This calculation assumes a conservative estimated standard deviation of 25, true geometric mean of 20 and a half width confidence interval of 8. The current number of participants in the sub-study (503) will provide a sufficient sample assuming participants are evenly distributed across the 3 groups. The addition of Group 3 will create 4 possible dosing cohorts, based on the how many doses of 300mg AZD7442 received prior to entering Group 3 and whether or not this was followed by a further two doses of 600mg AZD7442:

Group 1

- Cohort 1: AZD7442 300 mg, 300 mg

Group 2

- Cohort 2: Placebo, AZD7442 300 mg, 300 mg

Group 3

- Cohort 3 (from Group 1): AZD7442 300 mg, 300 mg, 600 mg, 600 mg
- Cohort 4 (From Group 2): Placebo, AZD7442 300 mg, 600 mg, 600 mg

9.3 Populations for Analyses

The following populations are defined in Table 14.

Table 14 Populations for Analysis

Population/Analysis set	Description
Safety analysis set	The safety analysis set consists of all participants who have received at least one dose of IMP in the sub-study.
Safety pre-exposure analysis set	The safety pre-exposure analysis set will include all participants in the safety analysis set who were not SARS-CoV-2 RT-PCR-positive at baseline in the parent study.
Pharmacokinetic analysis set	All participants in the safety analysis set who received AZD7442 and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post dose will be included in the PK analysis dataset.

IMP, investigational medicinal product; PK, pharmacokinetic; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2; severe acute respiratory syndrome-coronavirus 2.

9.4 Statistical Analyses

All results will be summarized with descriptive statistics by cohort. Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate.

9.4.1 Safety: Primary Endpoint

9.4.1.1 Primary Endpoint(s)

The safety of AZD7442 will primarily be assessed by:

- Incidence of AEs
- Incidence of SAEs
- Incidence of MAAEs
- Incidence of AESIs

The AE severity will be graded according to Appendix B and coded using the most recent version of the Medical Dictionary for Regulatory Activities. Adverse events will be presented for each dosing interval group by system organ class and preferred term. Summaries will include the number and percentage of participants reporting at least one event, number of events, and exposure adjusted rates, where appropriate.

An overview of AEs will be presented for each group, including the number and percentage of participants with any AE and SAEs. Summaries will present the relationship to IMP as assessed by the Investigator, maximum intensity, seriousness, and death.

A listing will cover details for each individual AE.

9.4.1.2 Other Safety Endpoint(s)

- Laboratory parameters (hematology, clinical chemistry, coagulation, urinalysis, and cardiac biomarkers)
- 12-lead safety ECG
- Vital signs (blood pressure, pulse rate, oral temperature, and respiratory rate)
- Physical examination

Laboratory assessments will be performed for hematology, clinical chemistry, coagulation, urinalysis, and cardiac biomarkers parameters. Laboratory parameters will be graded using the most recent version of the CTCAE.

Additionally, per the SoA (Section 1.3), all participants will be evaluated via ECG, vital signs, and a targeted physical examination. All parameters from laboratory, ECG, vital signs, and physical examination assessments will be summarized with descriptive statistics based on data type (continuous, categorical, etc). No hypothesis testing or CIs will be performed or calculated, unless otherwise specified.

9.4.2 Secondary Endpoints

9.4.2.1 Pharmacokinetic

Individual AZD7442 (AZD8895 and AZD1061) serum concentration data will be listed and tabulated, along with descriptive statistics. Pharmacokinetic parameters (eg, AUC, $t_{1/2}$) may be estimated using non-compartmental analysis if data permit. Potential correlation between PK exposure and efficacy/safety response may be explored. The serum AZD8895 and AZD1016 concentration data will be analyzed using a population PK analysis approach to characterize the PK for the different dosing intervals and will be reported in a separate report.

9.4.2.2 Antidrug Antibodies

The incidence of ADA to AZD7442 will be assessed and summarized by number and percentage of participants who are ADA positive by dosing interval group. The ADA titer will be listed by participant at different time points. The impact of ADA on PK, pharmacodynamic, efficacy, and association with AEs and SAEs, will be assessed.

Participants who receive an a different COVID monoclonal antibody than AZD7442, 30 days prior to entering the sub-study will be excluded from this analysis set. In addition, samples collected after a participant receives another COVID monoclonal antibody may be excluded.

9.4.2.3 Neutralizing Antibodies

Descriptive statistics for GMTs and GMFR will include number of participants, geometric mean, GSD, 95% CI, minimum, and maximum.

The GMT will be calculated as the antilogarithm of $\Sigma(\log_2$ transformed titer/n), ie, as the antilogarithm transformation of the mean of the log-transformed titer, where n is the number of participants with titer information. The GSD for GMT will be calculated as the antilogarithm transformation of the standard deviation of the log-transformed titer. The 95% CI will be calculated as the antilogarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

The fold rise is calculated as the ratio of the post-dose titer level to the pre-dose titer level. GMFR will be calculated as antilogarithm of Σ (log_2 transformed (post-dose titer/pre-dose titer)/n). The GSD and 95% CIs for GMFR will be calculated similarly to those for GMT.

Participants who receive an a different COVID monoclonal antibody than AZD7442, 30 days prior to entering the sub-study will be excluded from this analysis set. In addition, samples collected after a participant receives another COVID monoclonal antibody may be excluded.

9.4.3 Exploratory Endpoints

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9.5 Interim Analyses

One interim analysis is planned to be conducted in this repeat dose sub-study. The interim analysis is planned after a minimum of 50 participants who received AZD7442 on Day 1 of the parent PROVENT study have received a repeat dose of AZD7442 on SS-D1 and been followed until SS-D29 (ie, for 28 days after their second dose of AZD7442). The interim analyses will assess the primary safety endpoint and available secondary endpoints. Additional interim analyses may be conducted to generate additional data as required.

9.6 Data Safety Monitoring Board

The independent DSMB monitoring the PROVENT parent study will provide oversight, to ensure safe and ethical conduct of the sub-study.

The DSMB will make any necessary recommendations to the Sponsor based on their evaluations of emerging data. The first Data Review Meeting will occur in conjunction with the first interim analysis as specified in Section 9.5. Subsequent Data Review Meetings will be held in line with the DSMB Charter. The DSMB will also review sub-study progress and

monitor for evidence of harm resulting from AZD7442. If required, the DSMB will recommend temporarily stopping or termination of the sub-study.

For details on the DSMB, refer to Appendix A 5. Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

9.7 Adjudication Committees

9.7.1 Morbidity Adjudication Committee

An independent Morbidity Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of blinded data to evaluate whether the causes of death for participants are considered COVID-19 associated. All fatal events will be further assessed as part of safety evaluation. Further details of this adjudication will be provided in a separate Morbidity Adjudication Committee Charter.

9.7.2 Cardiovascular Event Adjudication Committee

An independent Cardiovascular Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of de-identified data to systematically evaluate cardiovascular events. The adjudicated cardiovascular events will be included in descriptive analyses of safety data. Further details of the Cardiovascular Event Adjudication Committee composition, operation, and listings of preferred terms to identify events are provided in a separate Cardiovascular Event Adjudication Committee Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This sub-study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, protocol addendum, ICF, IB, 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 sub-study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a 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 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of the IMP 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 the IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB/IEC, and Investigators.
- For all studies, except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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 an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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 one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the sub-study to the participant or his/her legally authorized representative or equivalent representative as locally defined and answer all questions regarding the sub-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. Participants or their legally authorized representative or equivalent representative as locally defined will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the sub-study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the sub-study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative or equivalent representative as locally defined.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use.

Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to Investigators.

Data and Safety Monitoring Board (DSMB)

The same external DSMB from the PROVENT parent study will monitor and protect the safety of the participants throughout the sub-study. The DSMB members were selected for their expertise. The voting members of the DSMB are external to AstraZeneca, including the DSMB chair. Summaries of data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants. The data for review will be outlined in the DSMB Charter and will be agreed to in advance by the DSMB members. The first Data Review Meeting will occur in conjunction with the interim analysis. Subsequent Data Review Meetings will be held in line with the DSMB Charter. Ad hoc meetings will be implemented if required. The DSMB will review safety data on a regular basis as set out in the DSMB Charter. Participant enrollment can continue during DSMB review of safety data. The available safety data for the participants will be evaluated by the DSMB. Safety summaries will be prepared prior to each Data Review Meeting. During the study, the benefit/risk assessment will be continuously monitored by the DSMB to ensure that the balance remains favorable.

The DSMB can recommend modifications of the sub-study protocol to enhance participant safety and to recommend temporarily stopping the study or early termination of the study if

there is strong evidence that AZD7442 or continuation of the study poses a safety concern to participants.

The independent DSMB monitoring the PROVENT parent study will provide oversight, to ensure safe and ethical conduct of the sub-study.

The DSMB will make any necessary recommendations to the Sponsor based on their evaluations of emerging data. The first Data Review Meeting will occur in conjunction with the first interim analysis as specified in Section 9.5. Subsequent Data Review Meetings will be held in line with the DSMB Charter. The DSMB will also review sub-study progress and monitor for evidence of harm resulting from AZD7442. If required, the DSMB will recommend temporarily stopping or termination of the sub-study.

For details on the DSMB, refer to Appendix A 5. Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

Morbidity Adjudication Committee

See Section 9.7.1

Cardiovascular Event Adjudication Committee

See Section 9.7.2.

A 6 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 7 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF, unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk-Based

Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the relevant study plans.

- The Sponsor or designee is responsible for the data management of this sub-study including, quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data review to confirm that data entered into the eCRF by authorized site personnel are accurate, and complete; that the safety and rights of participants are being protected; and that the sub-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 sub-study must be retained by the Investigator for 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

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

A 9 Study and Site Start and Closure

The first act of recruitment is the first participant screened in the PROVENT parent study 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 IMP development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(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 10 Publication Policy

- The results of this sub-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 multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

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

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 IMP 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 fulfills one or more of the following criteria:

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

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

Life-threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

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

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

Severity Rating Scale (Adapted from CTCAE v5.0):

- 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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology, such as the underlying disease, other drugs, other host, or environmental factors.
- 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 recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if, following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data, including enough information to make an informed judgment. With limited or 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

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca IMP 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 recognized that could have led to an error

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

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature

- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - including those that led 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
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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 earlier.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The Investigator:

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

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

Exempt - Substances that 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 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; eg, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (eg, 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 $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

AST or ALT $\geq 3\times$ ULN **together with** TBL $\geq 2\times$ 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 $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

If Central Laboratories are Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met; where this is the case, the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results, the Investigator, will without delay:

- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

If Local Laboratories are Being Used:

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

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

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria not met

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

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

D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within one day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to 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 3 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 AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

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

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine

whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory Tests

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

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT (Gamma glutamyl transpeptidase) LDH Prothrombin time INR
Viral hepatitis	IgM (immunoglobulin M) anti-HAV HBsAg IgM and IgG (immunoglobulin G) anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal antibody (Anti-LKM) Anti-Smooth Muscle antibody (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.
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

Appendix E Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

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

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP (see number 3 below for definition) 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 participant (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch, flush, swollen lips, tongue and/or uvula)
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP (see number 3 below for definition) or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3 Reduced BP after exposure to known allergen for that participant (minutes to several hours); for adults a systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline BP (taken at or immediately prior to start of the IMP administration), whichever BP is lower.

The following definitions are provided for the purposes of this study:

Hypersensitivity reaction: An acute onset of an illness with involvement of the skin, mucosal tissue, or both after injection of IMP (but does not meet the definition of anaphylaxis described above).

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

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

Severity of symptoms	Treatment	Investigational product
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 site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mmHg change in systolic BP from pre-administration measurement.	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: • 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.	Pause or hold additional IMP injection immediately. At the discretion of the Investigator, resume current IMP administration under observation.
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 IMP administration immediately. At the discretion of the Investigator, resume current IMP administration under observation.

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

Severity of symptoms	Treatment	Investigational product
Moderate hypersensitivity reactions Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with > 20 mmHg 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 IMP administration immediately.

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

Severity of symptoms	Treatment	Investigational product
Severe Above plus fever with rigors, hypo- or hypertension with ≥ 40 mmHg 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	Evaluate participant, including close monitoring of vital signs. 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	Stop IMP administration immediately. Do not resume current dosing. Permanently discontinue IMP 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; IMP, investigational medicinal product; IV, intravenously; PO, per os (by mouth); SC, subcutaneously; SOC, standard of care.

Appendix F Abbreviations

Abbreviation or special term	Explanation
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
AUC	area under the plasma concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BP	Blood pressure
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug Induced Liver Injury
DNA	deoxyribonucleic acid
DP	drug product
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic Case Report Form
EUA	Emergency Use Authorization
FSH	Follicle-stimulating hormone
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GMFR	geometric mean fold rise
GMT	geometric mean titer
GSD	geometric standard deviation
HL	Hy's Law
IB	Investigator's Brochure
IATA	International Airline Transportation Association

Abbreviation or special term	Explanation
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
MAAE	medically attended adverse event
mAbs	monoclonal antibodies
nAb	neutralizing antibody
NP	nasopharyngeal
PHL	Potential Hy's Law
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic(s)
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SoA	Schedule of Activities
SS-D	sub-study day
TBL	total bilirubin level
USA	United States of America
ULN	upper limit of normal
WHO	World Health Organization

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