Clinical Study Protocol	
IMP	AZD7442
Study Code	D8850C00002
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A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19

Sponsor Name:	**AstraZeneca AB**
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Regulatory Agency Identifier Number(s):	IND number: 150712 EudraCT Number: 2020-004356-16

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

Protocol Number: D8850C00002

Amendment Number: Amendment 9.0

IMP: AZD7442

Study Phase: Phase III

Short Title: Phase III Double-blind, Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adults

Acronym: PROVENT: Prophylaxis Prevention

Study Physician Name and Contact Information will be provided separately

International Co-ordinating Investigator: Dr. Myron J. Levin

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 10.0 [Amendment 9]	01 December 2021
Version 9.0 [Amendment 8]	26 July 2021
Version 8.0 [Amendment 7]	29 June 2021
Version 7.0 [Amendment 6]	07 April 2021
Version 6.0 [Amendment 5]	18 March 2021
Version 5.0 [Amendment 4]	12 February 2021
Version 4.0 [Amendment 3]	21 December 2020
Version 3.0 [Amendment 2]	13 November 2020
Version 2.0 [Amendment 1]	26 October 2020
Original Protocol	07 October 2020

Version 10.0, 01 December 2021
Key amendment and rationale for change: The following changes have been made: An addendum has been added to include a sub-study to the Phase III PROVENT study: '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)' (D8850C002A01). The 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 levels associated with protection against COVID-19. Participants at a sub-set of active PROVENT parent study sites in participating countries will be invited to enroll in this sub-study (N=500). The conduct of the parent study will not change for those participants who are not included in the sub-study.

Section 1.3 (Schedule of Activities)

A footnote has been added to Table 2 regarding an expanded visit window for the Day 366 Visit for participants entering the sub-study.

Section 2.3.1 (Risk Assessment): Information about cardiovascular events in the PROVENT study has been added.

Section 4 (Overall Design):
The procedure for participants transitioning from the parent study to the sub-study is described.

Section 8.3.4 (Adverse Events of Special Interest)

The following adverse events of special interest have been added to the study: cardiac ischemia, cardiac failure, and thrombotic events.

Previous amendments are summarized in Appendix I.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety, and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19

Short Title: Phase III Double-blind, Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adults

Rationale: AZD7442, a combination of 2 mAbs (AZD8895 and AZD1061) is being evaluated for administration to prevent or treat the Coronavirus Disease 2019 (COVID-19). This Phase III study will assess the efficacy of AZD7442 for the pre-exposure prophylaxis of COVID-19 in Adults.

Objectives and Endpoints:

Objective	Estimand Description/Endpoint
Primary	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183	**Population:** Full pre-exposure analysis set
	Endpoint: A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.
	Intercurrent events: Participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for the primary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (ie, intercurrent events will be handled using a while on treatment strategy).
	Summary measure: Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo	AEs, SAEs, MAAEs, and AESIs post dose of IMP.
Key Secondary	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection	**Population:** Full pre-exposure analysis set
	Endpoint: The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.

Objective	Estimand Description/Endpoint
	Intercurrent events: Participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for this endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (ie, intercurrent events will be handled using a while on treatment strategy).
Secondary	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP.
To assess the pharmacokinetics of AZD7442 administered as a single dose of 300 mg IM	Serum AZD7442 concentrations. PK parameters if data permit.
To evaluate ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; PK, pharmacokinetic; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically attended adverse event; RT-PCR, reverse transcriptase polymerase chain reaction; 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, randomized, double-blind, placebo-controlled, multi-country, multi-center study assessing the safety and efficacy of a single dose of AZD7442 (× 2 IM injections) compared to placebo for the prevention of COVID-19. Approximately 100 sites will participate in this study.

Participants will be adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment (see Section 5.1). Participants will be enrolled into one of 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age. All such participants will be considered as being at increased risk for inadequate response to active immunization on the basis of age

(presumed immunosenescence). Cohort 1 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by residence in a long-term care facility or not.

- Cohort 2: Adults < 60 years of age. Cohort 2 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by risk of exposure to infection with SARS-CoV-2.

Approximately 5150 participants will be randomized in a 2:1 ratio to receive a single dose (× 2 IM injections) of either 300 mg of AZD7442 (n = approximately 3433) or saline placebo (n = approximately 1717) on Day 1. Participants will be enrolled into the study in 2 stages, contingent upon safety: approximately 300 participants in Stage 1, followed by approximately 4850 participants in Stage 2.

To allow for the assessment of clonal material, 150 participants in the US will receive the clonal material or placebo in a 2:1 ratio. The participants will be recruited according to the current inclusion and exclusion criteria and will be followed as per the schedule of activities. A PK analysis will be performed of pooled versus clonal material.

Following a screening period of ≤ 7 days, participants will receive a single dose (× 2 IM injections) of IMP. After administration of the dose of IMP on Day 1, participants will undergo follow-up for 15 months (until Day 457).

Disclosure Statement: This is a parallel-group preventive study with 2 arms that is double-blind.

Number of Participants: Enrollment of approximately 5150 participants in 2 stages is planned, contingent upon safety:

- Stage 1 (N = 300 [at least 150 from Cohort 1]: 200 to AZD7442, 100 to placebo). The first 15 participants (Sentinel Cohort), will undergo safety monitoring for 4 hours post IMP administration before dosing the rest of the participants in Stage 1. The remaining 285 participants will undergo safety monitoring for 2 hours post IMP administration.
- Stage 2 (N = 4850: 3233 to AZD7442, 1617 to placebo). Stage 2 will start only after an independent DSMB has confirmed it is appropriate to proceed. The DSMB will evaluate 7-day safety data from participants dosed in Stage 1. If hypersensitivity reactions are observed during Stage 1, safety monitoring 2 hours post IMP administration will be implemented for Stage 2; otherwise the minimum safety monitoring time will be 1 hour. If the study is suspended or the decision is made not to proceed from Stage 1 to Stage 2, a protocol amendment will be submitted to Health Authorities.

Note: 'Enrolled' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned in the study, are considered 'screen failures'.

Intervention Groups and Duration: Participants will be randomized in a 2:1 ratio to receive one single 300 mg dose of AZD7442 (divided in 2 sequential IM injections, one for each mAb component) or saline placebo. Investigational medicinal product will be administered on Day 1, and participants will be monitored for up to one year after IMP administration.

Data Safety Monitoring Board: An independent DSMB will confirm it is appropriate to proceed to Stage 2 after evaluating 7-day safety data from participants dosed in Stage 1.

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.

Statistical Methods

Primary Endpoint: The primary efficacy endpoint is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.

Sample Size: Approximately 5150 participants will be randomized in a 2:1 ratio to receive a single IM dose of AZD7442 (divided into 2 sequential injections, one for each mAb component) (the active group, n = approximately 3433) or saline placebo (divided into 2 sequential injections) (the control group, n = approximately 1717) on Day 1.

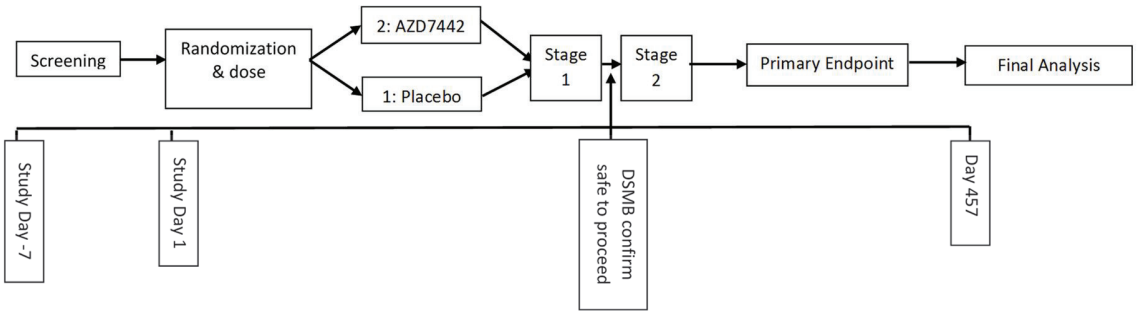
The sample size calculations are based on the primary efficacy endpoint and were derived following a modified Poisson regression approach (Zou 2004). All participants will be followed for the entire duration of the study. With at least 18 observed events, assuming 80% true efficacy, the study will have approximately 90% power to demonstrate that the lower bound of the 2-sided 95% CI for efficacy is greater than 0.

Primary Analysis Timing: The primary analysis will be conducted after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded (at which point the ability to observe primary endpoint events is expected to have diminished), whichever occurs earlier. All primary endpoint events accrued up until the data cut-off will be included in the primary analysis.

A final analysis will be conducted at the end of the study, ie, when the last participant dosed has completed the Day 457 visit.

1.2 Schematic

Figure 1 Study Design



Following screening (-7 to 0 days), randomization will occur in 2 stages and is contingent on safety. The planned primary analysis will occur after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs first. A final analysis is planned when all participants complete the study (Day 457).
DSMB, Data Safety Monitoring Board

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening Period

Procedure / Study Day	Day -7 to Day 1 [a]	For details, see section:
Informed consent: Main study, including optional genetic sample and analysis	X	5.1, 8.7
Assignment SID number	X	
Demographics and Risk Categorization	X	5.1
Medical history	X	
Virology: Hepatitis B surface antigen, hepatitis C virus antibody; HIV-I and HIV-II[b]	X	8.2.4.2
Complete physical examination, including height and weight	X	8.2.1
Vital signs (including pulse oximetry)	X	8.2.2
NP swab for SARS-CoV-2 RT-PCR[c] (local or central laboratory)	X	8.6.1.1
Completed rapid point of care SARS-CoV-2 serology testing using serum sample	X	8.5.2.2
Serum chemistry[b]	X	8.2.4
Hematology[b]	X	8.2.4
Urinalysis[b]	X	8.2.4
Coagulation[b]	X	8.2.4
Triplicate 12-lead ECG	X	8.2.3
Pregnancy test (WOCBP only)[d]	X	8.2.4.1
FSH (suspected postmenopausal women, <50 years)[e]	X	8.2.4.1
Assessment of SAEs	X	8.3
Concomitant medications	X	6.5
Verify eligibility criteria	X	5.1, 5.2

[a] Screening activities may be collected over more than one visit if necessary; if screening and dosing occur at the same visit, only one evaluation is required, unless otherwise specified.
[b] Baseline measure not included in eligibility assessment.
[c] Sample to be collected for testing not earlier than Day -7. Result not required prior to randomization or dosing. If local laboratory is unavailable the central laboratory may be used.
[d] If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.
[e] 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.

AE, adverse event; β-hCG, beta-human chorionic gonadotropin; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; SID, subject identification; WOCBP, women of childbearing potential.

Table 2 Schedule of Activities: Treatment and Follow-up Period – Main Study

Procedure	Treatment and Follow-up Period								Early Discontinuation visit	For details, see section:
Day	**1**	**8**	**29**	**58**	**92**	**183**	**366**	**457**		
Window (days)	**NA**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15[a]**	**± 15**		
Medical history	X									
Targeted physical examination	X	X	X	X	X	X	X		X	8.2.1
Vital signs (including pulse oximetry)	X[b] (post dose)	X	X	X	X	X	X		X	8.2.2
Triplicate 12-lead ECG							X		X	8.2.3
Serum chemistry	X	X	X	X	X	X	X		X	8.2.4
Hematology	X	X	X	X	X	X	X		X	8.2.4
Urinalysis	X	X	X	X	X	X	X		X	8.2.4
Pregnancy test – urine (WOCBP only)[c]	X (predose)	X	X	X	X	X	X		X	8.2.4.1
Concomitant medications	X	X	X	X	X	X	X		X	6.5
Verify eligibility criteria	X									5.1, 5.2
Genomics initiative optional, exploratory genetic sample	X (predose)									8.7
IMP administration	X									6.1
Efficacy assessments										
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms[d]	←	—	—	—	—	—	—	→		8.1.1
NP swab for SARS-CoV-2 RT-PCR (central laboratory)	X[e] (predose)									8.6.1.1

Table 2 Schedule of Activities: Treatment and Follow-up Period – Main Study

Procedure	Treatment and Follow-up Period								Early Discontinuation visit	For details, see section:
Day	**1**	**8**	**29**	**58**	**92**	**183**	**366**	**457**		
Window (days)	**NA**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15[a]**	**± 15**		
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing	X (predose)	X	X	X	X	X	X		X	8.5.2.2
Pharmacokinetics, pharmacodynamics, and ADA assessments										
Serum sample for AZD7442 pharmacokinetic assessment	X (predose)	X	X	X	X	X	X	X [optional]	X	8.5.1
Serum sample for AZD7442 ADA assessment	X (predose)		X	X		X	X	X [optional]	X	8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment	X (predose)	X	X	X	X	X	X	X [optional]	X	8.5.3.1
Serum sample exploratory biomarkers	X (predose)	X	X	X	X	X	X		X	8.5.2.5
Participant subset only: Nasal adsorption for exploratory assessments[f,g]	X	X			X	X	X		X	8.5.2.3
At viable sites only: PBMCs for B and T cell responses[h]	X									8.5.2.4
Safety assessments										
Check injection sites[i]	X									8.2.5
AEs[j]	←	—	—	—	—	—	—	→	X[k]	X	8.3
SAEs, MAAEs, and AESIs[j]	←	—	—	—	—	—	—	→	X[k]	X	8.3
Telephone contact for safety monitoring[l]	←	—	—	—	—	—	—	→			8.3

[a] For participants entering the sub-study, this visit window is extended to ± 2 months.

[b] Perform 15 minutes (± 5 minutes) after both injections are complete.
[c] If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.
[d] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.
[e] Baseline sample, not a screening sample; results not needed prior to dosing.
[f] When test supplies are available, sampling should be performed.
[g] Completed for a subset of approximately 300 participants from select US sites enrolling Cohort 1 and 2.
[h] To be collected when operationally viable.
[i] Perform immediately, 30 minutes (± 10 minutes) after both injections are complete, and prior to participant release.
[j] **Stage 1**: The first 15 participants will be monitored for safety for 4 hours after IMP administration; the following 285 participants will be monitored for 2 hours after IMP administration. **Stage 2**: If hypersensitivity reactions occur during Stage 1 participants will be monitored for 2 hours after IMP administration; otherwise the minimum safety monitoring time would be 1 hour post IMP administration.
[k] AEs, SAEs, MAARs and AESIs may be assessed via a phone call at Day 457.
[l] For the first 4 days after IMP administration, the first 15 participants will be contacted daily for safety monitoring followed by weekly contact. All other participants will be contacted weekly. During weekly contact the investigator will enquire about any COVID-19 symptoms from the past 7 days.

Ab, antibody; ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; ECG, electrocardiogram; MAAE, medically attended adverse event; NA, not applicable; nAb, neutralizing antibody; NP, nasopharyngeal; 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; US, United States; WOCBP, women of childbearing potential.

Table 3 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									
Digital health device[d]	←	—	—	—	—	—	—	→	8.1.5
Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary)	←	—	—	—	—	—	—	→	8.1.6
Saliva sample for viral shedding[e]	X	X	X	X	X	X	X	X	8.6.1.2
Nasopharyngeal swab									
SARS-CoV-2 RT-PCR (local laboratory)[f]	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,g]	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 3 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[h]	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 will continue with the Illness Visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the digital health device.

[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] Digital health device: A wearable health device with biosensor. Measures will include skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity.

[e] To be collected when operationally viable.

[f] 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.

[g] PBMCs will be collected from up to approximately the first 1000 participants on IL-D1 visit.

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

Note: The Illness Visit schedule is to be performed in addition to the Main Study Visit schedule, where visits coincide all assessments from the Main Study schedule and Illness Visit schedule should be performed.

AESI, adverse events of special interest; COVID-19, coronavirus disease 2019; D, day; ECG, electrocardiogram; MAAE, medically attended adverse event; NA, not applicable; nAb, neutralizing antibody; NP, nasopharyngeal; 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

SARS-CoV-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 29 September 2020, has resulted in 33,206,004 confirmed cases of COVID-19, including 999,239 deaths, reported to WHO (WHO 2020). Unlike the majority of coronaviruses that cause mild disease in humans and animals, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia. This is also a characteristic of the genetically-similar SARS-CoV and the more distantly related MERS-CoV, both of which were responsible for prior outbreaks in 2002 to 2003 and 2012, respectively (Gorbalenya et al 2020).

Effective interventions to prevent or treat COVID-19 remain limited in number and clinical experience is limited. Clinical management is limited to supportive care, consequently overwhelming resources of healthcare systems around the world.

As a response to the ongoing pandemic, AstraZeneca is developing mAbs to the SARS-CoV-2 S protein. The SARS-CoV-2 S protein contains the virus's RBD, which enables the virus to bind to receptors on human cells. By targeting this region of the virus's S protein, antibodies can block the virus's attachment to human cells, and, therefore, is expected to block infection. Amino acid substitutions have been introduced into the antibodies to both extend their half-lives, which should prolong their potential prophylactic benefit, and decrease Fc effector function in order to decrease the potential risk of antibody-dependent enhancement of disease.

AZD7442, a combination of 2 of these mAbs (AZD8895 and AZD1061), is being evaluated for administration to prevent and/or treat COVID-19. There is currently one ongoing Phase I study with AZD7442.

For further details, please refer to the AZD7442 IB.

2.1 Study Rationale

AZD7442, a combination of 2 mAbs (AZD8895 and AZD1061) is being evaluated for administration to prevent or treat COVID-19. This Phase III study will assess the efficacy of AZD7442 for the pre-exposure prophylaxis of COVID-19 in adults.

2.2 Background

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. One fourth of their genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly, while the S protein is involved in receptor binding, mediating virus entry into host cells during coronavirus infection via different receptors (Li 2016). SARS-CoV-2 belongs to the phylogenetic lineage B of the

genus Beta-coronavirus and it recognizes the ACE2 as the entry receptor (Zhou et al 2020). It is the seventh coronavirus known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

2.2.1 Summary of Nonclinical Pharmacology

AZD7442 neutralizes SARS-CoV-2 by mAbs AZD8895 and AZD1061 binding to unique, non-overlapping epitopes on the RBD of the viral S protein, which is responsible for receptor-binding and cellular fusion. Both AZD8895 and AZD1061 bind the RBD with nanomolar affinity and are individually capable of sterically blocking the virus from engaging its cellular receptor human angiotensin-converting enzyme-2. This binding translates to potent inhibition of SARS-CoV-2 infection by AZD7742 in vitro, with half-maximal inhibitory concentration (IC_{50}) values between 10 and 26 ng/mL.

A combination mAb approach, like AZD7442, is advantageous because SARS-CoV-2 is an RNA virus capable of mutating, and the combination provides redundancy in case a viral mutation confers resistance to one of the mAbs. In vitro studies confirm that viruses with reduced susceptibility to AZD8895 or AZD1061 individually remain susceptible to the combination. The combination also demonstrated synergy in in vitro neutralization assays.

The Fc region of both AZD8895 and AZD1061 has been engineered to include YTE and TM amino acid substitutions to extend $t_{1/2}$ and reduce Fc effector function, respectively. These substitutions resulted in an expected increase in binding affinity to FcRn at pH 6.0 and reduced binding to FcγR and complement proteins involved in antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and other antibody-directed effector functions. Importantly, incorporation of these YTE and TM substitutions did not alter the potency of AZD7442 in vitro.

The parental mAbs of AZD8895 (COV2-2196) and AZD1061 (COV2-2130), which lack Fc substitutions, provided protection from SARS-CoV-2 infection in vivo. Prophylactic administration of the mAbs alone or in combination, at a 10 mg/kg dose, resulted in attenuated weight loss, as well as reduced viral RNA levels in the lungs of mice challenged with SARS-CoV-2. Similarly, reduced viral RNA levels were measured in the lungs of mice when mAbs were administered 12 hours after infection at a 20 mg/kg dose. The reduction in viral titers correlates with a reduction in proinflammatory cytokines and alveolar damage in the lungs of infected mice.

Finally, intravenous administration of AZD7442 protected rhesus macaques from SARS-CoV-2 infection. NHPs that received an isotype mAb three days prior to SARS-CoV-2 infection demonstrated mean viral sgmRNA in nasal mucosae and bronchoalveolar lavage that peaked at approximately 5 log10 copies/swab or 5 log10 copies/mL, respectively. In contrast, NHPs prophylaxed with either a 4 or 40 mg/kg dose of AZD7442 had little or no detectable

levels of viral sgmRNA in both nasal mucosae and lungs. In the treatment arm of the study, intravenous administration of a 40 mg/kg dose of AZD7442 one day after SARS-CoV-2 infection resulted in rapid resolution of virus infection in both the nasal mucosae and lungs of infected NHPs. While viral sgmRNA was detected up to 10 days after infection in control animals, AZD7442 administration resulted in undetectable levels of viral sgmRNA by Day 4 post-infection in the lungs and Day 7 post-infection in the nasal mucosae, showing that AZD7442 can provide clinical benefit even with administration after virus infection.

Collectively, these data demonstrate that the mAbs that comprise AZD7442 potently neutralize SARS-CoV-2 in vitro and are efficacious in animal challenge models when administered prophylactically or therapeutically.

2.2.2 Summary of Nonclinical Pharmacokinetics and Drug Metabolism

A preliminary assessment of the PK properties of AZD8895 and AZD1061, the 2 component mAbs of AZD7442, was conducted by in vivo comparisons against a similar AstraZeneca-developed mAb, MEDI8897 (nirsevimab). Similar to AZD8895 and AZD1061, MEDI8897 is a human IgG1κ mAb directed against a viral fusion protein (F protein of RSV) and contains the YTE amino acid substitutions in its Fc region to prolong its $t_{1/2}$. Unlike MEDI8897, AZD8895 and AZD1061 additionally contain a second triple amino acid substitution, L234F/L235E/P331S (TM), in their Fc regions, intended to inhibit FcγR binding. Following IV injection in Tg32 mice, the PK of MEDI8897+TM was similar to that of MEDI8897, indicating the TM did not significantly affect the PK of MEDI8897. The PK of AZD8895 and AZD1061 were similar to those of MEDI8897 and MEDI8897+TM. In the 8-week cynomolgus monkey GLP toxicology study for AZD7442, high exposures were achieved and were consistent across animals and between males and females for both AZD8895 and AZD1061, for both the 300 mg/kg IV dose and the 75 mg/kg IM dose. The exposures were as expected since the AZD7442 TK was similar to the TK of nirsevimab in cynomolgus monkeys based on 1-week post single dose TK data available for nirsevimab.

Human efficacious doses for AZD7442 were evaluated using in vitro functional potency data (virus-neutralizing activity of AZD7442 against SARS-CoV-2) and PK data. In addition, a viral dynamic model was developed, which allowed for understanding of the pharmacodynamic effects of AZD7442 to inhibit a SARS-CoV-2 infection and the resulting immune response. The viral dynamic model indicates that virus entry inhibition greater than approximately 80% is sufficient to prevent infection. Therefore, doses were selected that result in concentrations in serum and the ELF of the lungs above the in vitro derived inhibition parameter of IC_{80} (inhibiting SARS-CoV-2 by 80%) of 104 ng/mL (4 × IC_{50} of 26 ng/mL) for a duration of at least 5 months post-dose. Assuming a partition ratio of 1% for lung ELF-to-serum and the IC_{80} of 104 ng/mL, an IM dose of 300 mg is expected to provide prophylactic coverage at least 5 months and this dose would also be effective to treat active infection with

significant reduction in peak viral load and complete suppression of viral load earlier than accomplished by the acquired immune response only.

The doses tested in the monkey toxicology study (75 mg/kg per antibody for IM and 300 mg/kg per antibody for IV) were determined to be no-observed-adverse-effect level (NOAEL). These NOAELs were used to calculate the safety margins for the clinical doses in the FTIH study (Study D8850C00001) by dividing the NOAEL mean exposure (C_{max} or AUC) over the first 56 days post dose in the monkeys by the geometric mean exposure (C_{max} or AUC) over the first 60 days post-dose for each clinical dose cohort. The calculated margins using either AUC or C_{max} are shown in Table 4 for the IM clinical dose relative to the IM NOAEL and for the IV clinical doses relative to the IV NOAEL.

Table 4 Safety Margin Prediction for the Dose Levels in Phase I Study D8850C00001

Route of Administration in FTIH	FTIH AZD7442 Dose (mg)	GLP Monkey Toxicology Study AZD7442 Dose (mg/kg)	Safety Margin AUC (0-60 days)	Safety Margin C_{max}
IM	300	150	33	62
IV	300	600	67	150
IV	1000	600	22	49
IV	3000	600	7.5	16

AUC, area under plasma concentration-time curve; $C_{max,}$ maximum plasma concentration; FTIH, first-time-in-human; GLP, Good Laboratory Practice; IM, intramuscular; IV, intravenous

2.2.3 Summary of Toxicology

Due to the foreign nature of the S RBD antigen target for the 2 antibodies in AZD7442 and lack of S protein expression in human or animal tissues, no pharmacologically relevant species is available for nonclinical safety testing of AZD7442. Therefore, in accordance with ICH S6 (R1), only a short term, ie, a single IV and IM dose, study of the combination (AZD7442) in cynomolgus monkeys with a 2- and 8-week follow-up, and a TCR study assessing binding of the combination (AZD7442) and the individual antibodies (AZD8895 and AZD1061) to the full list of human and cynomolgus monkey tissues are being conducted. The single dose study in cynomolgus monkeys is ongoing, and interim result summaries are available for Week 2 and Week 8 (end of study). At the Week 2 interim assessment, there were no AZD7442-related changes in clinical signs, injection site observations/dermal scoring, body weights, qualitative food consumption, ophthalmology, veterinary physical examinations, ECGs, neurologic examinations, blood pressure and heart rate, respiration rates, body temperature, clinical pathology parameters (hematology, coagulation, and urinalysis/urine chemistry), gross necropsy findings, organ weights, or histopathologic examinations. Based on the Week 2 assessment, the single dose administration of AZD7442

via intravenous infusion was well tolerated in cynomolgus monkeys at a dose level of 600 mg/kg (combination of 300 mg/kg of AZD8895 and 300 mg/kg of AZD1061). A limited summary of the available Week 8 end of study data covering clinical signs, body weight, clinical pathology, organ weights, and macroscopic findings at necropsy, confirms the tolerability demonstrated at the Week 2 interim assessment. In the TCR study, the assessment of the combination (AZD7442), and the individual components AZD8895 and AZD1061, was completed on the full list of tissues from 3◦independent human and cynomolgus monkey donors. No binding to any tissues was observed, confirming the absence of target and off-target binding in humans and cynomolgus monkeys.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD7442 is provided in the AZD7442 IB.

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

There are no identified risks associated with AZD7442. No observations are considered to represent expected adverse reactions that would form part of an emerging safety profile.

As of the data cut-off date of 03 November 2020, there have been no events of anaphylaxis or other serious allergic reactions in the FTIH Phase I Study D8850C00001. No injection site reactions occurred in participants dosed IM, 10 participants in the AZD7442 300 mg IM group and 2 participants in the placebo IM group.

AZD7442 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 S protein for neutralization of the virus. Neither mAb has any human target. There are no potential risks based on mechanism of action.

Potential risks are associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs.

The important potential risks associated with the administration of immunoglobulin, include, but are not limited to, anaphylaxis and other serious hypersensitivity reactions including immune complex disease.

Other potential risks include, but are not limited to, injection site reactions, infusion-related reactions, and ADE disease.

Antibody-dependent enhancement of disease is a theoretical risk. Two different syndromes exist: 1) ADE, which involves increased binding efficiency of virus-antibody complexes to Fc

receptor bearing cells and which triggers virus entry. The mAbs in AZD7442 have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of ADE occurring via this mechanism should range from very low to none. 2) VAERD, which is a distinct clinical syndrome that occurred in young children in the 1960s when whole inactivated virus vaccines for measles and RSV were tested. Immunizing with limiting doses of RSV antigen, especially with conformationally incorrect antigens, can result in 2 major types of immunological phenomena: a) A relatively high ratio of antibody that binds, but does not neutralize, virus could potentially result in immunogenic cell death and complement activation (leading to inflammation and airway obstruction); b) immunization with whole inactivated virus vaccines can result in allergic inflammation characterized by, eg, increased mucus production, airway hyperresponsiveness, and attenuated cytolytic T cell activity (T helper 2 cell immune response). This mechanism, induced by vaccines, should not be provoked by mAbs.

A small number of cardiovascular serious adverse events (myocardial infarction and cardiac failure) have been reported in the PROVENT 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. Cardiovascular events will be monitored in the PROVENT study (see Section 4.1.1).

In a separate Phase III AZD7442 study STORM CHASER (N = 1121), which enrolled a younger population with fewer baseline cardiac risk factors than PROVENT, no cardiac SAEs have been reported.

2.3.2 Benefit Assessment

Recipients of AZD7442 do not have any guaranteed benefit, however, AZD7442 may be efficacious and offer participants protection from COVID-19.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this 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 5 Objectives and Endpoints

Objective	Estimand Description/Endpoint
Primary	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183	**Population:** Full pre-exposure analysis set
	Endpoint: A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.
	Intercurrent events: Participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product but, in both cases prior to having met the criteria for the primary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (ie, intercurrent events will be handled using a while on treatment strategy).
	Summary measure: Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo	AEs, SAEs, MAAEs, and AESIs post dose of IMP.
Key Secondary	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection	**Population:** Full pre-exposure analysis set
	Endpoint: The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.
	Intercurrent events: Participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for this endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (ie, intercurrent events will be handled using a while on treatment strategy).
Secondary	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP.

Table 5 Objectives and Endpoints

Objective	Estimand Description/Endpoint
To assess the pharmacokinetics of AZD7442 administered as a single dose of 300 mg IM	Serum AZD7442 concentrations. PK parameters if data permit.
To evaluate ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum.
Exploratory	
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366.
To evaluate the single dose pharmacokinetic concentrations of AZD7442 in nasal fluid	AZD7442 nasal concentrations.
To determine anti-SARS-CoV-2 nAb levels in serum following a single IM dose of AZD7442 or placebo	Post-treatment GMTs and GMFRs from baseline value through Day 457 after single IM dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo neutralization assay).
To quantify SARS-CoV-2 viral loads in infected participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Viral genome copies in NP swabs at Illness Visits as determined by qRT-PCR.
To quantify duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Duration of SARS-CoV-2 shedding in saliva over time.
To characterize resistance to AZD7442 (Illness Visits)	Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 variants to AZD7442.
To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Biophysical parameters, including, but not limited to, serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from Illness Visits Day 1 through Day 28.
To assess symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only)	Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28.
To assess additional immune responses following a single IM dose of AZD7442 or placebo	Other exploratory assays for humoral, mucosal and cellular immune responses may be performed based upon emerging safety, efficacy, and pharmacodynamic data.

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 rises; IM, intramuscular; IMP, investigational medicinal product; nAb, neutralizing antibody; NP, nasopharyngeal; qRT-PCR, quantitative real-time polymerase chain reaction; 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, randomized, double-blind, placebo-controlled, multi-country, multi-center study assessing the safety and efficacy of a single dose of AZD7442 (× 2 IM injections) compared to placebo for the prevention of COVID-19. Approximately 100 sites will participate in this study.

Participants will be adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment. Participants will be enrolled into one of 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age. All participants will be considered as being at increased risk for inadequate response to active immunization on the basis of age (presumed immunosenescence). Cohort 1 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by residence in a long-term care facility or not.
- Cohort 2: Adults < 60 years of age. Cohort 2 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by risk of exposure to infection with SARS-CoV-2.

Approximately 5150 participants will be randomized in a 2:1 ratio to receive a single IM dose of either 300 mg of AZD7442 (n = approximately 3433) or saline placebo (n = approximately 1717) on Day 1.

Enrollment will occur in 2 stages (Figure 2), which is contingent upon evaluation of 7-day safety data of Stage 1 enrollment by an independent DSMB and its recommendation to proceed with Stage 2:

- Stage 1 (n = 300 [at least 150 from Cohort 1]: 200 to AZD7442, 100 to placebo). The first 15 participants (Sentinel Cohort) will undergo safety monitoring for 4 hours post IMP

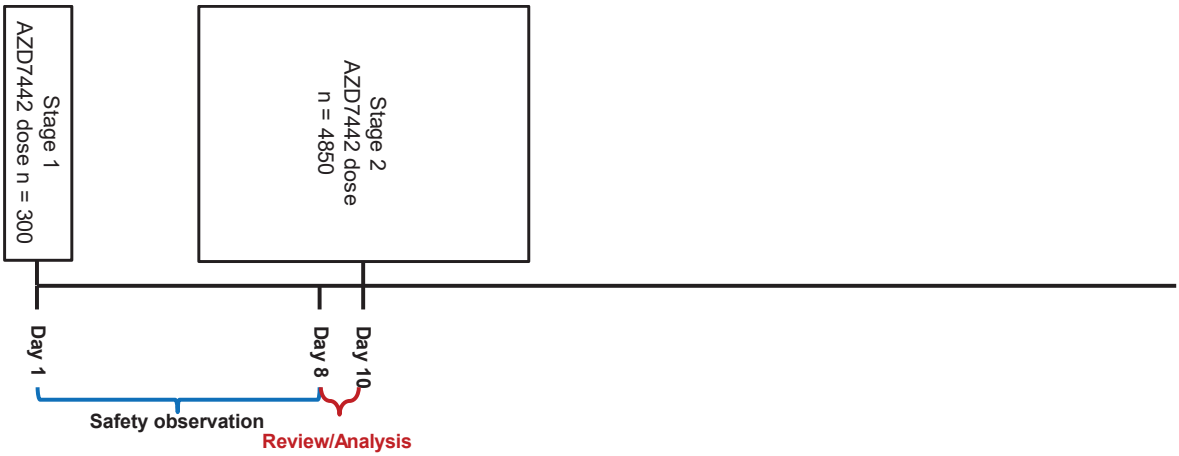
administration before dosing the rest of the participants in Stage 1. The remaining 285 participants will undergo safety monitoring for 2 hours post IMP administration.

- Stage 2 (n = 4850: 3233 to AZD7442, 1617 to placebo). Stage 2 will start only after an independent DSMB has confirmed it is appropriate to proceed. The DSMB will evaluate 7-day safety data from participants dosed in Stage 1. If hypersensitivity reactions are observed during Stage 1, safety monitoring for 2 hours post IMP administration will be implemented for Stage 2; otherwise, the minimum safety monitoring time will be 1 hour. If the study is suspended or the decision is made not to proceed from Stage 1 to Stage 2, a protocol amendment will be submitted to Health Authorities.

To allow for the assessment of clonal material, 150 participants in the US will receive the clonal material or placebo in a 2:1 ratio. The participants will be recruited according to the current inclusion and exclusion criteria and will be followed as per the schedule of activities. A PK analysis will be performed of pooled versus clonal material (see Section 9.4.4).

Following a screening period of ≤ 7 days, participants will receive a single dose (× 2 IM injections) of IMP. After administration of the dose of IMP on Day 1, participants will undergo follow up for up to 15 months (until Day 457).

Figure 2 Study Dose Exposure Expansion



4.1.1 PROVENT repeat dose sub-study

Participants (N=500) at a subset of active PROVENT parent study sites in participating countries may be invited to enroll in a Phase III open-label sub-study (D8850C002A01) to assess the safety, PK, and immunogenicity of repeat doses of AZD7442. The sub-study population will target specific participants who may benefit from a repeat dose of AZD7442. The details of the sub-study will be derived from the PROVENT parent study and are provided in an addendum to the CSP. 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. Participants who have not yet completed their Day 366 Visit in the parent study will be unblinded and undergo a combined Day 366 Visit and SS-D1 Visit as part of the sub-study procedures. Pre-dose Day 366 assessments will serve as baseline assessments for the sub-study.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Endpoints

The primary efficacy endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. Participants will be included in the primary endpoint if they have RT-PCR-confirmed SARS-CoV-2 and meet the qualifying symptoms (see Section 8.1.1).

The efficacy endpoints in this study are analogous to endpoints used for evaluating the efficacy of influenza vaccines. These definitions have 4 components: (1) a definition of clinical illness; (2) a method of respiratory specimen sampling for the detection of associated shedding of the relevant virus; (3) an assay method for laboratory confirmation; and (4) a defined surveillance period.

The primary efficacy endpoint pre-specifies an efficacy evaluation period of 182 days post dose (ie, through Day 183). This timeframe is based on the anticipated elimination half-life of the dose and on in vitro and nonclinical virus neutralization data which suggest that AZD7442's efficacy will be waning after 182 days or 26 weeks (ie, the duration of protection by AZD7442 is expected to be 26 weeks). To mitigate the impact of rapid roll out of authorized COVID-19 vaccines and the subsequent increasing numbers of unblinded and/or vaccinated participants on the statistical integrity of the study, the primary analysis will be conducted before all participants have been followed through Day 183 and will result in variable follow-up times.

The key secondary efficacy endpoint captures the incidence of participants with a post-baseline SARS-CoV-2 nucleocapsid post-baseline antibody response, which will enable the assessment of whether or not AZD7442 prevents asymptomatic infections as well as symptomatic infections.

4.2.2 Rationale for 7-day Safety Evaluation

An evaluation of 7-day safety data from participants dosed in Stage 1 will be performed by an independent DSMB, who will advise the Sponsor on whether it is appropriate to proceed into Stage 2 of the study. Furthermore, because the Phase I studies included younger volunteers (aged < 60 years), and recognizing the vulnerability of participants aged ≥ 60 years,

AstraZeneca will ensure that at least 50% of the 300 participants enrolled in Stage 1 will be from Cohort 1.

Only safety data will be considered at this stage. Adverse events associated with exogenous immunoglobulins as a class, ie, infusion reactions, hypersensitivity reactions, including anaphylaxis, and injection site reactions, typically manifest within minutes to hours; and rarely after 24 hours. For such events, 7 days of observation should be sufficient for detection.

Further support for this approach is evidenced by previous experience in assessing the safety of IgG1 mAbs with either YTE or TM substitutions in clinical trials:

AstraZeneca mAbs containing the YTE substitutions:

- MEDI8897 (nirsevimab) (anti-RSV; completed Phase I study in healthy adults in [Griffin et al 2017]; Phase Ib/IIa study in preterm infants in [Domachowske et al 2018]; Phase IIb pivotal study in preterm infants in [Griffin et al 2020]). Granted Breakthrough Therapy Designation by the FDA in 2019 and PRIME eligibility by the EMA in 2019
- MEDI4893 (suvratoxumab) (anti-*Staphylococcus aureus* alpha toxin, completed Phase II). MEDI4893 was granted Fast Track Designation for the prevention of pneumonia caused by the bacterium *Staphylococcus aureus* in 2014
- Motavizumab-YTE (anti-RSV, completed Phase I study in healthy volunteers) (Robbie et al 2013).

AstraZeneca mAbs that contain TM substitutions:

- Durvalumab (IMFINZI™, approved for non-small cell lung cancer, extensive-stage small cell- lung cancer, urothelial cancer; Imfinzi USPI, [Antonia et al 2018])
- Anifrolumab (anti-interferon alpha receptor, 2 Phase III lupus studies completed, marketing applications planned for 2020; [Furie et al 2019, Morand and Furie 2020])
- Oleclumab (anti-CD73; several oncology clinical studies ongoing).

AstraZeneca considers that the data gathered in the Phase I and II studies for both MEDI4893 (mAb that binds the *Staphylococcus aureus* alpha toxin; suvratoxumab) and MEDI8897 (mAb that binds the RSV fusion protein; nirsevimab) support using early safety data to initiate future studies with AZD7442. Like AZD7442, both antibodies do not have human host cell targets, and both mAbs also have the YTE substitutions introduced for $t_{1/2}$ extension. Safety follow-up in both studies was for one year, which is also the planned safety follow-up period for AZD7442. In general, in both programs, the safety profile of the mAbs, whether administered IV or IM, was similar to that seen for placebo.

In the MEDI4893 Phase I study, the incidence of treatment-emergent AEs was not elevated in participants who received the mAb compared to placebo participants. In addition, no Grade 3 or higher treatment-emergent AEs or treatment-emergent SAEs were recorded, and no participants discontinued from the study due to a treatment-emergent AE.

In the MEDI4893 Phase II study, 100 participants received placebo, 15 received MEDI4893 2000 mg, and 96 received MEDI4893 5000 mg. MEDI4893 was well tolerated, with similar types and frequencies of treatment-emergent AEs reported in MEDI4893 and placebo participants. Overall, 90.0% of participants in the placebo group and 91.9% of participants in the MEDI4893 total group had at least 1 AE. AEs were considered to be treatment-related by the investigator in 2.0% of participants in the placebo group and 9.0% of participants in the MEDI4893 total group. Events of ≥ Grade 3 severity occurred at similar rates in both the placebo and MEDI4893 total groups (51.0% vs 53.2%). SAEs were reported in 32 participants (32.0%) in the placebo group and 40 participants (36.0%) in the MEDI4893 total group. Of the participants with SAEs, 2 participants (1 each in the MEDI4893 2000 mg and MEDI4893 5000 mg groups) had events that were deemed treatment-related. Thirty-two deaths (16 in each of the placebo and MEDI4893 total groups) were reported during the study through Day 31. AESIs and NOCDs were reported only in the MEDI4893 groups. AESIs occurred in 7 participants (4 in the 2000 mg group and 3 in the 5000 mg group), of whom 4 participants had treatment-related events. Three participants (2 in the 2000 mg group and 1 in the 5000 mg group) had AESIs of ≥ Grade 3 severity. NOCDs were reported in 2 participants in the MEDI4893 5000 mg group.

In the MEDI8897 Phase I study, the overall incidence of treatment-emergent AEs was similar in mAb recipients compared to placebo recipients, and while there were 3 events that were classified as either Grade 3 or higher treatment-emergent AEs or as treatment-emergent SAEs in participants who received 300 mg of MEDI8897 IM (eye injury, gunshot wound, and appendicitis), these events were not considered related to receipt of IMP. No participants discontinued from the study due to a treatment-emergent AE.

In the MEDI8897 Phase IIb study, 968 participants received MEDI8897 versus 479 received placebo. The types and frequencies of adverse events that occurred during the trial were similar in the nirsevimab and placebo groups. Overall, 86.8% of participants in the placebo group and 86.2% of participants in the MEDI8897 group had at least 1 AE. AEs that occurred ≤ 1 day post dose were observed in 2.5% of participants in both groups. In comparison to the placebo group, the MEDI8897 group had a lower incidence of AEs occurring ≤ 7 days post dose (15.2% vs 12.5%, respectively), AEs ≥ Grade 3 in severity (12.5% vs 8.0%, respectively), and SAEs (16.9% vs 11.2%, respectively). Five deaths (3 in the placebo group and 2 in the MEDI8897 group) were reported during the study through Day 361. One additional participant in the placebo group died on Day 367. None of these deaths were considered related to IMP by the investigator. Overall, the incidence of treatment-related AEs

(placebo 2.1%, MEDI8897 2.3%), AESIs (hypersensitivity, immune complex disease, and thrombocytopenia; placebo 0.6%, MEDI8897 0.5%); skin hypersensitivity reactions (placebo 0.6%, MEDI8897 0.5%), and NOCDs (placebo 0.8%, MEDI8897 0.4%) was low and generally comparable between the placebo and MEDI8897 groups.

4.3 Justification for Dose

The dose level, 300 mg IM, selected for this study is based on PK of nirsevimab in adult Phase I study, a mAb that neutralizes the respiratory syncytial virus (Griffin et al 2017) with similar PK to AZD7442 in animals, and on nonclinical in vitro and in vivo pharmacology data showing the effects of AZD7442 against SARS-CoV-2.

For further details, please refer to the AZD7442 IB.

4.4 End of Study Definition

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

The end of the 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 study only if all of the following criteria apply:

Age

1 Participant must be ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Candidate for benefit from passive immunization with antibodies, defined as:

(a) Increased risk for inadequate response to active immunization (predicted poor responders to vaccines) (Furer et al 2020, Poland et al 2018, Wagner and Weinberger 2020, Zimmermann and Curtis 2019), defined as:

- Elderly, ie, ≥ 60 years old
- Obese, ie, BMI ≥ 30
- Congestive heart failure
- Chronic obstructive pulmonary disease

- Chronic kidney disease, ie, GFR < 30 mL/min/1.73 m^2 (Lamb et al 2013)
- Chronic liver disease
- Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines
- Intolerant of vaccine. Defined as previous history of severe adverse event or serious adverse event after receiving any approved vaccine.

(b) Increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment. Examples include:

- Health care workers, including staff of long-term care facilities (including skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults)
- Workers in industrial settings shown to have been at high risk for SARS-CoV-2 transmission, including but not limited to meatpacking plants
- Military personnel residing or working in high density settings including but not limited to barracks, ships, or close-quarters working environments
- Students living in dormitory settings
- Others living in settings of similar close or high-density proximity

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

4 Negative result from point of care SARS-CoV-2 serology testing 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 Day 1 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 Day 1 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 at Visit 1 and throughout the study as indicated per the SoA (see Section 1.3).

Examples of highly effective birth control methods are listed in Table 6.

Table 6 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 that 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.

Table 6 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods

[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.

Informed Consent

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

7 If able, signed informed consent. Ensure that participants who are considered by the investigator clinically unable to consent at screening and who are entered into the study by the consent of a legally acceptable representative show evidence of assent, as applicable in accordance with local regulations. See Appendix A for further details.

5.2 Exclusion Criteria

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

Medical Conditions

1 Significant infection or other acute illness, including fever > 100°F (> 37.8°C) on the day prior to or day of randomization.

2 History of laboratory-confirmed SARS-CoV-2 infection or any positive SARS-CoV-2 result based on available data at screening.

3 History of infection with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

4 Known history of allergy or reaction to any component of the study drug formulation.

5 Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.

6 Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 or expected receipt during the period of study follow-up.

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

8 Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data.

Prior/Concurrent Clinical Study Experience

9 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study (see Table 8).

Other Exclusions

10 For women only - currently pregnant (confirmed with positive pregnancy test) or breast feeding.

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

12 Employees of the Sponsor involved in planning, executing, supervising, or reviewing the AZD7442 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

13 In nations, states, or other jurisdictions that for legal or ethical reasons bar the enrollment of participants who lack capacity to provide their own informed consent, such subjects are excluded.

5.3 Lifestyle Considerations

- Participants must follow the contraception requirements outlined in Section 5.1.
- Restrictions relating to concomitant medications are described in Section 6.5.
- Agree to wear digital health device if diagnosed with COVID-19 as described in Section 8.1.5.

5.3.1 Lifestyle Restrictions

5.3.1.1 Women of Non Childbearing Potential

Women of non-childbearing potential are defined as female participants who are permanently surgically sterilized or postmenopausal.

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy at least 6 weeks before screening. Bilateral oophorectomy alone is acceptable only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

For women aged < 50 years, postmenopausal is defined as having both a history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment, and an FSH level in the postmenopausal range. 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.

5.3.1.2 Women of Childbearing Potential

A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Women of childbearing potential who are sexually active must agree to use, with their non-sterilized male partner, an approved method of highly effective contraception from the time of IMP administration until 365 days after the dose of IMP. In instances where a WOCBP participant, has a sterilized male partner, the vasectomized partner must have received a medical assessment of surgical success (Table 6). Women should be stable on their chosen method of birth control for at least one month before dosing.

Highly effective contraception is summarized in Table 6.

Pregnancy Testing

Women of childbearing potential can be included only after a negative urine pregnancy test. Urine pregnancy testing will be done as per the SoA (see Section 1.3). If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.

Pregnancy

If the participant becomes pregnant during the study, this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study, but confirmed after completion of the study. The pregnancy will be followed, and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed. Pregnancy occurring and reported during the study will be followed up for safety from the post-dose administration to end of the study, or until term, to identify pregnancy outcome, whichever is later. Female participants who become pregnant after dosing will continue to have all safety PK (serum and nasal), ADA serum sample, and nAb samples collected. These do not represent a safety risk, and serum samples are already being collected as part of safety follow-up. Any complications during the planned follow-up of any pregnant participant (if any) will be discussed between the PI and AstraZeneca, and a decision to halt or continue any further sampling will be made on a case by case basis.

Ova Donation

Female participants should not donate ova for the duration of the study and for at least 365 days after the IMP dose.

5.3.1.3 Male Participants

To avoid transfer of fluids to a sexual partner, all male participants must use a condom starting from the time of IMP administration until 365 days after dosing. Contraception for female partners of childbearing may be considered, but is not required for this protocol.

Sperm Donation

Male participants should not donate sperm for the duration of the study and for at least 365 days after the dose of IMP.

Pregnancy

Participants will be instructed that if their partner becomes pregnant during the study, this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study, but confirmed after completion of the study. In the event that a participant's partner is subsequently found to be pregnant after the participant is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed, and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility. Only a single rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening. Individuals who are rescreened do not need to reconsent for the study.

6 STUDY INTERVENTION

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

The third party medical device used for assessment of COVID-19 symptoms (ie, digital health device [Section 8.1.5]) is not considered a study intervention.

6.1 IMP(s) Administered

6.1.1 IMP

Participants will be randomized in a 2:1 ratio to receive one single 300 mg dose of AZD7442 (divided in 2 sequential injections, one for each mAb component) or saline placebo (Table 7). Investigational medicinal product will be administered on Day 1, and participants will be monitored for up to 15 months after IMP administration.

A dose of AZD7442 consists of 2 IM injections. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, the second IM injection should not be given. For details on the treatment of anaphylactic reactions after IMP IM injections see Appendix F. For further details on IMP discontinuation, see Section 7.1.

Table 7 Investigational Products

Intervention name	AZD7442 (AZD8895 + AZD1061)	Placebo (not to be matched to AZD7442)
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.	0.9% (w/v) saline
Unit dose strength(s)	300 mg AZD7442 consisting of 150 mg AZD8895 and AZD1061 at 100 mg/mL	0.9% (w/v) saline solution for injection
Dosage level(s)	300 mg single dose of AZD7442 (150 mg of AZD8895 and 150 mg of AZD1061)	Single dose
Route of administration	2 IM injections of 1.5 mL each	2 IM injections of 1.5 mL each
Use	Experimental	Placebo-comparator
Sourcing	AZD7442 (AZD8895 + AZD1061): AstraZeneca.	0.9% (w/v) saline solution supplied by study site.

Table 7 Investigational Products

Packaging and labeling	IMP will be provided in a glass vial. Each glass vial will be labeled as required per country requirement.	Not applicable

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 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 DPs, AZD8895 and AZD1061, to be administered sequentially.

Liquid DP

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 unblinded 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.

Use a separate disposable syringe with a 22 – 25 gauge and 1 – 1.5 in (25 – 38 mm) length needle 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 into an appropriately sized latex-free disposable polypropylene or polycarbonate syringe. Attach labels to the IM syringes to maintain blinding. 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.

Dose Preparation and Administration for Placebo

The dose of placebo (0.9% w/v saline solution) for administration must be prepared by the Investigator's or site's designated IMP manager using aseptic technique.

Use a separate disposable syringe with a 22 – 25 gauge and 1 – 1.5 in (25 – 38 mm) length needle for each placebo injection. Each injection should be administered as a separate single injection and administered sequentially. Intramuscular doses should be prepared by accurately withdrawing 1.5 mL volume of placebo into an appropriately sized latex-free disposable polypropylene or polycarbonate syringe. Attach labels to the IM syringes to maintain blinding.

Placebo should be administered according to standard practice procedures for IM injections, with one injection in each gluteal region. Placebo does not contain preservatives and any unused portion must be discarded.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

All participants will be centrally assigned to a randomized IMP using an IRT. Before the study is initiated, user guides, the log-in information, and directions for the IRT will be provided to each study site. Randomization will be stratified within each of the 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age. All participants will be considered as being at increased risk for inadequate response to active immunization on the basis of age (presumed immunosenescence). Cohort 1 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by residence in a long-term care facility or not.
- Cohort 2: Adults < 60 years of age. Cohort 2 will be capped, not to exceed 80% of total participants randomized. Within this cohort, randomization will be stratified by risk of exposure to infection with SARS-CoV-2 (see Inclusion Criterion 2b, Section 5.1).

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.

6.3.2 Blinding

Neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the IMP received. Because AZD7442 and placebo are visually distinct prior to dose preparation (due to differences in container closure), IMP will be handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site. Syringe masking will be required in order to maintain the blind.

The IRT will provide the investigator(s) or pharmacists a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to the Sponsor, without revealing the treatment given to the participant to the Sponsor staff.

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

6.3.3 Procedures for Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded IMP will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind.

All participants may receive, at their discretion, a COVID-19 vaccine, see Section 6.5.1.

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 re-dosing is permitted.

6.5 Concomitant Therapy

Permitted, restricted, and prohibited medications are summarized in Table 8.

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, 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 8 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 beginning > 30 days after IMP dose. Vaccines for the prevention of SARS-CoV-2 or COVID-19 are not considered routine vaccines in this protocol (see Section 5.2).
	Allergen immunotherapy	Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Visit 1 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.
	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.	
Prohibited	Not applicable	Not applicable
Restricted	Contraceptive methods	See Section 5.1.
	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; IMP, investigational medicinal product; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

6.5.1 COVID-19 Vaccines

- When an individual becomes eligible for the nationally deployed COVID-19 vaccine and it is locally available, they will be able to be unblinded on request, after a fully informed, objective discussion based on all available up-to-date information, and remain in the study.

  - Unblinded participants who received placebo should be advised that no study-associated contraindication to receiving a vaccine exists.
  - Unblinded participants who received AZD7442 should be advised that the 300 mg dose may provide 6 to 9 months of protection, but that this has not yet been demonstrated. In these participants, there would be little or no urgency for receiving a vaccine. In addition, in the presence of adequate neutralizing antibody titers, an appropriate and effective response to the vaccine could be impaired. Such participants should be advised to consider waiting an appropriate length of time (6 to 9 months) before receiving an anti-SARS-CoV-2 vaccine. For AZD7442, 6 to 9 months will represent 2 or 3 elimination half-lives of the mAbs, after which the potential for the mAbs to protect against COVID-19 should be reduced, and after which their potential interference with a vaccine may be reduced.
- For participants who have received IMP (blinded) and develop symptomatic COVID-19 at some point in the study:
  - There is no reason to believe that administration of a vaccine during acute COVID-19 will ameliorate the illness.
  - In almost all placebo recipients, and in most mAb recipients, an infection-induced immune response will occur, and this response should be protective. At this time, there is no reason to believe that the protection afforded by natural infection is less frequent or less robust than the protection provided by a vaccine, so the benefit of vaccination may be limited.
  - The risk of receiving a vaccine after resolution of the illness should be low.

Participants who receive a COVID-19 vaccine may continue in the study for safety follow-up.

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 4.4).

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 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. 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The 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 randomized, 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 two or more participants, within the first 300 participants, experience a grade III or higher hypersensitivity reaction.
- If two or more participants, within the first 300 participants, experience a grade III or higher injection site reaction.

In such a situation, no additional participants will be randomized or treated with IMP until review by the DSMB is complete (see Appendix A 5).

If the study is suspended or the decision is made not to proceed from Stage 1 to Stage 2, a protocol amendment will be submitted to Health Authorities.

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

8.1.1 Monitoring COVID-19 Symptoms

To determine the incidence of infection, study sites will contact participants weekly (telephone/email/text) through Day 366 with reminders to monitor for COVID-19 symptoms. During these weekly contacts the investigator will enquire about any COVID-19 symptoms (see Table 9) from the past 7 days 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 9, must contact the study site.

Participants who present with a COVID-19 qualifying symptom(s) after Day 1 will be instructed to initiate Illness Visits and will be tested locally for SARS-CoV-2 (see Section 8.6.1.1). If positive, the participant will be instructed to continue Illness Visits. If negative, the participant will be instructed to stop Illness Visits and continue with the main scheduled assessments (ie, Table 2). If positive, the participant will have additional assessments per Table 3. 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 9 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)

Table 9 COVID-19 Qualifying Symptoms

Participant must present with at least one of the following symptoms:	
Duration	**Symptom**
	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 2020)
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 (SpO_2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher.

Table 10 WHO Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected, no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy[a]	4

Table 10 WHO Clinical Progression Scale

Patient State	Descriptor	Score
	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

(Marshall et al 2020)

[a] If hospitalized for isolation only, record status as for ambulatory patient.

ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; NIV, non-invasive ventilation; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation

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 3); 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. SARS-CoV-2 RT-PCR results 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, including home collection requirements and digital health device and Illness e-Diary recordings. All devices and home lab kits should be brought to all subsequent Illness Visits. Participants who test negative for SARS-CoV-2 will be instructed to stop all Illness Visit assessments and return the digital health device and home lab kits. Participants will continue with follow-up visits per Table 2.

The Illness Visit schedule is to be performed in addition to the Main Study Visit schedule, where visits coincide, all assessments from the Main Study schedule and Illness Visit schedule should be performed.

To distinguish between the main study (Table 2) and the Illness Visits (Table 3), 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).

8.1.5 Digital Health Device

At IL-D1, participants will receive a wearable, digital health device (eg, Current Health Monitoring System) and be trained on use of the biosensor. The digital health device will continuously track biophysical parameters, including, but not limited to, serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity.

Data will be obtained from the biosensor and transmitted via a wireless hub from the participant to the vendor platform. The investigator can monitor participant vital signs and receive alerts if there are clinically significant changes. The data from the device are intended to provide an early indication of worsening health status that would allow the investigator to provide appropriate follow-up. The data are not intended to substitute for protocol-mandated standard safety monitoring, participant self-reporting, or investigator oversight.

Along with the device, participants will be provided with a paper-based Quick Start Guide containing general instructions for the device as well as frequently asked questions. A reference copy of the document will be retained in the Site Master File.

8.1.6 Illness e-Diary

An Illness e-Diary (See Appendix G) will be used to collect self-reported information about COVID-19-associated symptoms.

At the Day 1 Illness Visit, participants (or, if applicable, their caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) will be given access to the Illness e-Diary and trained by study staff on how to record the information and assess the severity of the symptoms.

Participants who test positive for SARS-CoV-2 will be instructed to continue recording in the Illness e-Diary until symptoms resolve or until the Day 28 Illness Visit. Participants who test negative will be instructed to stop Illness e-Diary recording.

Study sites will monitor the health status of participants via Illness e-Diary responses after the Day 1 Illness Visit, and will call participants as needed based on these responses.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

A complete physical examination will be performed at screening followed by targeted physical examinations as specified in the SoA (see Section 1.3).

- A complete physical examination will include, but not be limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history.
- A targeted physical examination will include areas suggested by the medical history. Each clinically significant abnormal finding following vaccination will be recorded as an AE.

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

8.2.2 Vital Signs

Vital signs, including heart rate, 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.

Data collected through the digital health device on heart rate, respiratory rate, temperature, and oxygen saturation level will be recorded as exploratory efficacy measurements and should not be reported as AEs, unless they result in an MAAE or SAE.

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

8.2.3 Electrocardiograms

A 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 PI 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 PI. 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 PI may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the PI 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, and urinalysis 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, and urinalysis 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 total bilirubin ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

8.2.4.1 Females Only

Pregnancy test (women of childbearing potential only)	
Serum human beta chorionic gonadotrophin (screening)	Urine human beta chorionic gonadotrophin (pre- and post-dose)
Pregnancy test (suspected postmenopausal women < 50 years only)	
Follicle-stimulating hormone (FSH)	

If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation. 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.

8.2.4.2 Viral Serology

Viral Serology	
Human immunodeficiency virus (HIV) I and II	Hepatitis C virus antibody
Hepatitis B surface antigen (HBsAg)	

Note: Virology at screening visit only

8.2.5 Injection Site Inspection

An injection site inspection will be performed according to Table 11 (see Section 1.3).

Table 11 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.

The first 15 participants (Sentinel Cohort) will undergo safety monitoring for 4 hours post IMP administration before dosing further participants. The next 285 participants will undergo safety monitoring for 2 hours pose IMP administration and, if no hypersensitivity reactions are observed, the remaining participants will undergo safety monitoring for 1 hour post IMP administration. Should hypersensitivity reactions be observed in the first 100 participants, all participants will be monitored for safety for at least 2 hours post IMP administration.

For the first 4 days after IMP administration the Sentinel Cohort will be contacted daily to monitor AEs.

8.3 Adverse Events and Serious Adverse Events

The PI 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.

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of a 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.

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 a 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

AESIs will be collected according to the time points specified in the SoA (see Section 1.3).

AESIs 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, including immune complex disease (Appendix F).
- Injection site reactions.
- Cardiac ischemia, cardiac failure, and thrombotic events

8.3.5 Medically Attended Adverse Events

MAAEs will be collected according to the time points specified in the SoA (see Section 1.3).

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

8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider, or reported in response to the open question from the study site staff: ‘Have you 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 DUS.

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 E 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 a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

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

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

8.3.10 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any IMP.

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 the dose.

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.

8.3.12 Device Deficiencies

Any deficiency observed with the digital health device (third-party medical device) will be collected and reported to the manufacturer by the investigators or other site personnel within one day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer. The manufacturer's medical device complaint report will be used to collect the deficiency.

8.4 Overdose

For this study, any dose of AZD7442 > 150 mg of either individual mAb will be considered an overdose.

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the PI 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 PI 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.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - 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 and Table 3.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to assess the PK of AZD7442. Samples collected for analyses of AZD7442 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped, as detailed in the Laboratory Manual.
- PK exposure (ie, AUCs) and other PK parameters, if data permit, will be calculated based on AZD7442 serum concentrations.

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.

Placebo samples will not be analyzed, unless there is a need to confirm that correct treatment has been given to study participants.

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

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

8.5.2 Immunogenicity Assessments

Serum samples for immunogenicity assessments will be collected according to Table 2 and Table 3. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Results for exploratory immunogenicity analyses may be reported separately from the CSR.

8.5.2.1 Anti-drug 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). A rapid point-of-care serology test will be utilized at screening to verify inclusion criteria. Baseline serostatus and the rate of SARS-CoV-2 infection in participants receiving AZD7442 versus placebo will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 N assay operated by an authorized laboratory.

8.5.2.3 Assessment of Mucosal Responses

Nasal samples to evaluate PK or SARS-CoV-2 antigen-specific antibody responses in nasal secretions will be collected from participants according to the SoA (see Section 1.3), when test supplies are available. A subset of 300 participants in the treatment arm from select United States sites enrolling Cohort 1 and Cohort 2 will be sampled at fixed time points of the main study (Table 2). All participants will be sampled at Illness Visits (Table 3). Nasal adsorption

specimens will be collected, when test supplies are available, by synthetic absorptive matrix sampling as outlined in the Laboratory Manual. AZD7442 nasal concentrations may be assessed using an appropriately qualified bioanalytical assay.

8.5.2.4 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing PBMCs isolated from select sites using methods that may include T-cell ELISpot assays to SARS-CoV-2 antigens, flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor as technical and/or operational feasibility allows.

Additionally, plasma will be isolated from the whole blood samples collected to isolate PBMCs, which may be utilized for exploratory immunogenicity and biomarker analyses as outlined in Section 8.6.2.

8.5.2.5 Additional Serum Immunogenicity

Additional serum samples for exploratory immunogenicity evaluation will be obtained according to the SoA (see Section 1.3). 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.

8.5.3 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 neutralizing antibodies to SARS-CoV-2 using validated wild-type neutralization assay or pseudo-neutralization assays.

8.6 Human Biological Sample for Biomarkers

8.6.1 Collection of mandatory samples for biomarker analysis

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

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. 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 immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

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

8.6.1.1 Virologic Assessments

Instructions for obtaining and processing NP swab samples are provided in the Laboratory Manual. NP swabs will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories. 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.

8.6.1.2 Assessment of Viral Shedding

Viral shedding will be assessed in saliva samples collected at site Illness Visits or self-collected at home, by an authorized RT-PCR assay for the qualitative and/or quantitative measurement of SARS-CoV-2.

8.6.2 Other Study-related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, PBMCs, or mucosal specimens to evaluate their association with observed clinical responses to AZD7442. Other study-related biomarker research excludes genetic analysis unless participant has consented to the Optional Genomics Initiative, Section 8.7.

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

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (see Section 1.3) and is subject to agreement in the Optional Genetic Research Information ICF.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples, see Appendix D.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183. Efficacy will be calculated as 1-relative risk, which is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group. The null hypothesis is: Efficacy of AZD7442 compared to placebo in preventing COVID-19 is equal to 0. Whereas, the alternative hypothesis is: Efficacy of AZD7442 compared to placebo in preventing COVID-19 is not equal to 0. That is:

- Null hypothesis: Efficacy = 0
- Alternative hypothesis: Efficacy $\neq$ 0

The primary efficacy endpoint will be formally assessed at the primary analysis, which will be conducted after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs first. All primary endpoint events accrued up until the data cut-off will be included in the primary analysis. The Type I error rate will be controlled by a 2-sided alpha = 0.05. At the primary analysis, efficacy will be presented with a 2-sided 95% CI, and statistical significance will be achieved if the lower bound of the 2-sided 95% CI is > 0. The success criterion for the study will be statistical significance.

9.2 Sample Size Determination

Approximately 5150 participants will be randomized in a 2:1 ratio to receive a single IM dose of AZD7442 (divided in 2 sequential injections, one for each mAb component) (the active group, n = approximately 3433) or saline placebo (the control group, n = approximately 1717) on Day 1.

The sample size calculations are based on the primary efficacy endpoint and were derived following a modified Poisson regression approach (Zou 2004). All participants will be followed for the entire duration of the study.

With at least 18 observed events, assuming 80% true efficacy, the study will have approximately 90% power to demonstrate that the lower bound of the 2-sided 95% CI for efficacy is greater than 0 (see Table 12).

Table 12 Simulated Power by Number of Observed Events

$\lambda_{Placebo}$	$\lambda_{AZD7442}$	Observed Events	Simulated Power
0.0074	0.0015	18	89%
0.0082	0.0016	20	96%
0.0090	0.0018	22	97%
0.0098	0.0020	24	98%

Simulated power is based upon 10000 simulations of trials assuming 80% efficacy $\left(1 - {}^{\lambda_{AZD7442}}/_{\lambda_{Placebo}} = 0.8\right)$, using Poisson regression model with robust variance, with no participants lost to follow-up. Power is the proportion of trials with p-value < 0.05.

The sample size necessary to achieve the power for the primary endpoint is calculated based on the assumed attack rate in the placebo group and the 80% efficacy assumption, using Poisson regression model with robust variance.

9.3 Populations for Analyses

The following populations are defined in Table 13.

Table 13 Populations for Analysis

Population/Analysis set	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomized participants who received at least one dose of IMP, irrespective of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent

Table 13 Populations for Analysis

Population/Analysis set	Description
	or assent to participate in the study will be included up to the date of their study termination.
Full pre-exposure analysis set	The full pre-exposure analysis set will include all participants in the full analysis set without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection.
Safety analysis set	The safety analysis set consists of all participants who have received at least one dose of IMP. Erroneously-treated participants (eg, those randomized to treatment A, but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who has on one or several occasions received active IMP is classified as active.
Pharmacokinetic analysis set	All participants 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.

9.4 Statistical Analyses

The primary analysis will occur after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded (at which point the ability to observe primary endpoint events is expected to have diminished), whichever occurs earlier. All primary endpoint events accrued up until the data cut-off will be included in the primary analysis (see Section 9.4.2.1). The date for the data cut-off for this analysis will be the date that the 24th primary endpoint event is confirmed or the date that 30% of study participants have become unblinded, whichever occurs earlier. All participants in the study will be assessed for efficacy for one year and safety for 15 months following the dose of IMP (Day 366 and Day 457, respectively). A final efficacy analysis will be conducted at the end of the study, ie, when the last participant dosed has completed the Day 457 visit.

The SAP will be finalized prior to the primary DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

The study will initially be completely double-blind until the primary analysis (ie, blind for participants, Investigators/site staff, and Sponsor/designated clinical research organization). To maintain the integrity of the study to allow rigorous evaluation of efficacy and safety through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study. The primary analysis will be carried out by an unblinded analysis team at AstraZeneca (or its delegates), and the procedure will be detailed in an

unblinding plan; Participant-level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented.

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.

All point estimates will be presented with a 95% CI, unless otherwise stated. P-values, corresponding to a 2-sided test, will be presented for comparisons between treatments. Methods for controlling multiplicity across endpoints are discussed in Section 9.4.5.

9.4.1 General Considerations

The primary efficacy analysis will be based on the double-blind, placebo-controlled phase of the study, and will compare participants randomized to receive a single IM dose of AZD7442 (× 2 IM injections) against participants randomized to saline placebo.

The primary estimand will be used for the analysis of the primary efficacy endpoint. It will be based on participants in the full pre-exposure analysis set, defined as all randomized participants who received at least one dose of IMP without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, analyzed according to their randomized treatment. For participants with multiple events, only the first occurrence will be used for the primary efficacy endpoint analysis. The set of intercurrent events for this estimand consists of participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the primary efficacy endpoint. The intercurrent events will be handled using a while on treatment strategy, where participants who experience an intercurrent event will be censored at the date of unblinding/receipt of first dose of COVID-19 product, whichever is earlier, within the primary estimand. Absence of data following participants' withdrawal prior to having met the primary efficacy endpoint will be treated as missing and participants will be considered as not having the event through the time of last observation. Deaths that are caused by COVID-19 and all hospitalizations due to COVID-19 will also be considered as primary efficacy endpoints.

An estimand using the treatment policy strategy, in which participants who become unblinded to treatment assignment will be included and analyzed regardless, will be used as the first of two key supportive analyses of the primary endpoint and will be included in the multiple testing hierarchy (Section 9.4.5). A second key supportive analysis, in which the endpoint is defined as first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP and prior to Day 183, will be performed and included in the multiple testing hierarchy. Additional estimands will be specified for the primary efficacy endpoint to

carry out sensitivity analyses for assessing the robustness of results. These sensitivity analyses will explore different methods for handling intercurrent events and different assumptions for missing data. Estimands will also be specified for the analysis of secondary endpoints. Full details will be provided in the SAP.

Demography and baseline characteristics will be summarized by treatment for the full analysis set and full pre-exposure analysis set. If there are major differences between the full pre-exposure analysis set and the safety analysis set, the summaries will be repeated and presented for the safety analysis set.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. Participants will be included in the primary endpoint if they have RT-PCR-confirmed SARS-CoV-2 and meet the qualifying symptoms summarized in Table 9.

If a participant's first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurs after Day 183, the participant will be considered as not having met the endpoint.

The primary efficacy endpoint is expected to be assessed at the primary analysis, after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs earlier. All primary endpoint events accrued up until the data cut-off will be included in the primary analysis.

As the primary efficacy analysis, the plan is to use the primary estimand and a Poisson regression model with robust variance (Zou 2004) to analyze the primary efficacy endpoint, which will include age (≥ 60 years, < 60 years) as a baseline covariate as well as the log of the follow-up time as an offset. The efficacy will be estimated from the model, which will give the RRR in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness. The efficacy is calculated as RRR = 100% × (1-relative risk), which is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group, expressed as a percentage. For primary analysis, the efficacy will be presented with a 2-sided 95% CI. Statistical significance will be achieved if the lower bound of the 2-sided 95% CI is > 0, which corresponds to a two-sided p-value < 0.05.

Two key supportive analyses of the primary endpoint will be conducted. The first will use a treatment policy strategy in which intercurrent events will be included and analyzed regardless. The second key supportive analysis will define the primary endpoint as the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP and prior to Day 183. These key supportive analyses are included in the multiple testing hierarchy.

Model assumptions will be checked and the robustness of the primary analysis will be assessed. The Poisson regression model with robust variance has the flexibility for exploring multiple imputation approaches using, eg, the observed placebo attack rate to impute missing data. Due to the potential limited number of events and the concern for model convergence due to empty cell, the primary analysis model will only include age group (≥ 60 years, < 60 years) as the covariate. Supplementary analysis including other additional covariates (eg, region) will be conducted to assess the robustness of the efficacy results, if data permit. If the Poisson regression model with robust variance fails to converge, an alternative approach will be implemented. Full details will be documented in the SAP.

To support the primary analysis, a Cox proportional hazard model will be fitted to the data as well as Kaplan-Meier curves presented for the active and control groups, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP prior to Day 183. In addition, the absolute risk reduction of AZD7442 over placebo in preventing the incidence of the SARS-CoV-2 RT-PCR-positive symptomatic illness and prior to Day 183 will be presented, along with the 2-sided 95% CI using the Miettinen and Nurminen's score method (Miettinen and Nurminen 1985). Full details will be documented in the SAP.

9.4.2.2 Secondary Endpoint(s)

The key secondary endpoint is the incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.

The key secondary efficacy hypothesis will be assessed at the primary analysis. Details on multiplicity control are provided in Section 9.4.5.

Other secondary endpoints include the following summary measures, derived from binary outcomes:

- The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post dose.
- The incidence of COVID-19-related Emergency Department visits occurring post dose.

Following the same methodology outlined for the primary endpoint, each of these secondary endpoints will be analyzed by a separate Poisson regression model with robust variance (Zou 2004), and they will include age as a baseline covariate. RRR will be estimated from each model, with a corresponding 95% CI. A p-value, corresponding to a 2-sided test, will be presented to compare AZD7442 against placebo. Except for the key secondary efficacy endpoint (whose alpha is protected under a hierarchical framework), the 95% CIs and p-values for other secondary endpoints will be nominal, as they are not controlled for multiplicity. To

support these analyses, descriptive statistics will be produced for the AZD7442 and control groups. Full details will be documented in the SAP.

9.4.2.3 Exploratory Endpoint(s)

Full details of the analyses for the exploratory endpoints will be specified in the SAP.

9.4.3 Safety

9.4.3.1 Primary Endpoint(s)

The safety of AZD7442 will primarily be assessed by:

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

AE severity will be graded according to Appendix B and coded using the most recent version of the Medical Dictionary for Regulatory Activities. AEs will be presented for each treatment 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 treatment 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. Full details of all AE analyses will be provided in the SAP.

9.4.3.2 Other Safety Endpoint(s)

- Laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis)
- 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, and urinalysis 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. Full details of safety endpoints analysis will be provided in the SAP.

9.4.4 Pharmacokinetic and Anti-drug Antibody

9.4.4.1 Pharmacokinetic

Individual AZD7442 (AZD8895 and AZD1061) serum concentration data will be listed and tabulated by treatment group, along with descriptive statistics. Pharmacokinetic exposure (ie, AUCs) and other PK parameters may be estimated using non-compartmental analysis, if data permit. Potential correlation between PK exposure and efficacy/safety response may be explored. Population PK analysis may be performed and reported in a separate report.

All participants included in the pharmacokinetic analysis set will be used to evaluate comparability between the clonal and pooled material.

PK parameters $AUC_{(0\text{-}91)}$ and C_{max} derived based on serum AZD7442 concentration measured at Day 1 (predose), Day 8, Day 29, Day 58, Day 92, Day 183, and Day 366 will be presented using non-compartmental methods by mAb component, material type (clonal versus pooled) and overall. Up to 3333 participants may have received pooled material and 100 participants clonal material at the time of the analysis. A comparison between material type will have greater than 90% power to reject the null hypothesis that the material is not equivalent with at least 70 participants per active group. The sample size calculations assume a difference of means test, $\alpha = 0.05$, CV = 0.4 and the null is rejected when the ratio of the log transformed means is below 0.8 or above 1.25. Concentration summary statistics and mean PK profiles will be listed and shown graphically for each mAb component.

9.4.4.2 Anti-drug Antibody

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

9.4.5 Methods for Multiplicity Control

A hierarchical approach will be used to control for multiplicity of the primary, key supportive, and key secondary efficacy analyses. That is, the null hypotheses for these efficacy analyses will be tested in a hierarchical order, and the subsequent null hypothesis will be tested at a significance level of 0.05 (2-sided) only if the prior null hypothesis is rejected (ie, the treatment effect on the efficacy endpoint is demonstrated at the significance level of 2-sided 0.05). The hierarchical approach will include the below analyses as ordered:

1 The primary efficacy endpoint will be assessed at the primary analysis, using the primary estimand, after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs earlier. All primary endpoint events accrued up until the data cut-off will be included in the primary analysis.
2 If the statistical significance of the primary efficacy endpoint is demonstrated at 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the first key supportive estimand (treatment policy strategy) will be conducted also at the primary analysis.
3 If the statistical significance of the first key supportive analysis of the primary endpoint is demonstrated at 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the second key supportive estimand (including death due to any cause) will be conducted also at the primary analysis.
4 If the statistical significance of the second key supportive analysis of the primary endpoint is demonstrated at 2-sided alpha of 0.05, a formal assessment of the key secondary efficacy endpoint will be conducted at the primary analysis.

With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

9.4.6 Sensitivity Analyses

Sensitivity analyses will be explored to assess the robustness of treatment effects for the primary efficacy endpoint, where different missing data mechanisms will be explored using multiple imputation approaches. Full details of the sensitivity analyses will be specified in the SAP, and documented prior to the primary DBL.

9.4.7 Subgroup Analyses

Subgroup analyses will be carried out to assess the consistency of the treatment effect across key, pre-defined, subgroups. These analyses will focus on the primary efficacy endpoint, and they may be performed on secondary and exploratory endpoints if deemed appropriate. The list of subgroups includes but may not be limited to: age, sex, region, race, ethnicity, comorbidity, and exposure risk (see Inclusion Criterion 2b, in Section 5.1). Full details of all subgroup analyses will be described in the SAP, including hypotheses that will be tested and the covariates and interaction terms to be included in the statistical models.

9.5 Interim Analyses

Not applicable.

9.6 Data Safety Monitoring Board

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study.

The DSMB will meet monthly and make any necessary recommendations to the Sponsor based on their evaluations of emerging data. In particular, the evaluation of 7-day safety data

from participants dosed in Stage 1 will be performed by the DSMB, who will advise the Sponsor on whether it is appropriate to proceed into Stage 2 of the study. The DSMB will also review study progress and monitor for evidence of harm resulting from AZD7442. If required, the DSMB will recommend temporarily stopping or termination of the study. There is no formal efficacy look by the DSMB with the potential for early stopping due to efficacy planned for this 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 Morbidity Adjudication Committee

An independent Morbidity Adjudication Committee will be constituted to 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. Only adjudicated deaths will be included in efficacy endpoints. 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.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 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 a 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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 study to the participant or his/her legally authorized representative or equivalent representative as locally defined and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. 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 study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative or equivalent representative as locally defined.

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

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

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

A 4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information 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)

An external DSMB will monitor and protect the safety of the participants throughout the double-blind treatment period of the study. The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Summaries of unblinded data will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants. The data for review will be outlined in the DSMB charter and will be agreed to in advance by the DSMB members. Data Review Meetings will be held monthly until last participant last visit to review data relating to participant safety and quality of study conduct. 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, including but not limited to, reviewing the 7-day safety data from all participants in the first dosing group of 300 participants prior to extension of dosing to the study's second group of 4700 participants. With the exception of the pause in study enrollment until safety data from the first dosing group of 300 participants has been reviewed by the DSMB, participant enrollment can continue during DSMB review of safety data. The available unblinded safety data for the randomized participants will be evaluated by the DSMB. Safety and efficacy summaries will be prepared prior to each Data Review Meeting. The efficacy summaries will

be presented for safety review purpose. During the study, the benefit/risk assessment will be continuously monitored by the DSMB to ensure that the balance remains favorable. Specifically, the study may be paused for DSMB review if a statistically significantly higher risk ratio (> 1), at the 1-sided 5% significance level, is seen for cases of severe COVID-19 in the AZD7442 arm compared to the placebo arm. This assessment for a potentially increased risk ratio will begin after 8 cases of severe COVID-19 have accrued in the study and will occur during each monthly DSMB data review or sooner if there are 5 or more severe cases accrued compared to the previous assessment. Based on the output of the review, the study could be paused for further evaluation of the potential signal. There is no formal efficacy look by the DSMB with the potential for early stopping due to efficacy planned for this study.

The DSMB can recommend modifications of the 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.

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 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 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 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 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 co-ordinating 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 judgement 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 a 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 judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may 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 judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or 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 a 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 a 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 DUS 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 Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in healthcare, and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participants' DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and, if a participant declines to participate, there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfill all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy volunteers and pediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Day 1 after randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction, replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The PI(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results, of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Any results generated from this genetic research will not be included in the CSR for the main study.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment, separate from the clinical database.

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

E 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.

E 2 Definitions

Potential Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

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

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

E 3 Identification of Potential Hy's Law Cases

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

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

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 E 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 E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 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.

E 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.

E 5 Review and Assessment of Potential Hy's Law Cases

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

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

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

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

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

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

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

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

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

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

E 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 judgement. 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.

E 7 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 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, generalised hives, pruritus or flushing, swollen lips, tongue and/or uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
- 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, generalised hives, itch, flush, swollen lips, tongue and/or uvula)
- Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
- 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 mm Hg 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 14, 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 SOC.

Table 14 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 localised 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 14 An Approach to Management of Anaphylactic, Hypersensitivity, and Post-injection Reactions

Severity of symptoms	Treatment	Investigational product
Moderate hypersensitivity reactions Reactions which may include generalised 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 14 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.

Appendix G e-Diary

1 Record your temperature. If you take more than one temperature, record the highest one (ie, ____ °F/°C).

(a) Free text input

Move to Question 2

2 Have you experienced shortness of breath?

(a) No

(b) Yes

If No, move to Question 4

If Yes, move to Question 3

3 Grade the severity of shortness of breath based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 4

4 Have you experienced difficulty breathing?

(a) No

(b) Yes

If No, move to Question 6

If Yes, move to Question 5

5 Grade the severity of the difficulty breathing based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 6

6 Have you experienced chills?

(a) No

(b) Yes

If No, move to Question 8

If Yes, move to Question 7

7 Grade the severity of chills based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 8

8 Have you experienced a cough?

(a) No

(b) Yes

If No, move to Question 10

If Yes, move to Question 9

9 Grade the severity of cough based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 10

10 Have you experienced fatigue?

(a) No

(b) Yes

If No, move to Question 12

If Yes, move to Question 11

11 Grade the severity of fatigue based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 12

12 Have you experienced muscle aches?
   (a) No
   (b) Yes

If No, move to Question 14

If Yes, move to Question 13

13 Grade the severity of muscle aches based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 14

14 Have you experienced body aches?
   (a) No
   (b) Yes

If No, move to Question 16

If Yes, move to Question 15

15 Grade the severity of body aches based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 16

16 Have you experienced headache?

(a) No

(b) Yes

If No, move to Question 18

If Yes, move to Question 17

17 Grade the severity of headache based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Repeated use of non-narcotic pain reliever

(c) 3 (Severe): Significant, any use of narcotic pain reliever or prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 18

18 Have you experienced new loss of taste?

(a) No

(b) Yes

If No, move to Question 20

If Yes, move to Question 19

19 Grade the severity of loss of taste based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 20

20 Have you experienced new loss of smell?

(a) No

(b) Yes

If No, move to Question 22

If Yes, move to Question 21

21 Grade the severity of loss of smell based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 22

22 Have you experienced a sore throat?
   (a) No
   (b) Yes

If No, move to Question 24

If Yes, move to Question 23

23 Grade the severity of sore throat based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 24

24 Have you experienced congestion?
   (a) No
   (b) Yes

If No, move to Question 26

If Yes, move to Question 25

25 Grade the severity of congestion based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 26

26 Have you experienced a runny nose?

(a) No

(b) Yes

If No, move to Question 28

If Yes, move to Question 27

27 Grade the severity of runny nose based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 28

28 Have you experienced nausea?

(a) No

(b) Yes

If No, move to Question 30

If Yes, move to Question 29

29 Grade the severity of nausea based on the descriptions below:

(a) 1 (Mild): No interference with activity

(b) 2 (Moderate): Some interference with activity

(c) 3 (Severe): Significant, prevents daily activity

(d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 30

30 Have you experienced vomiting?

(a) No

(b) Yes

If No, move to Question 32

If Yes, move to Question 31

31 Grade the severity of vomiting based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

Move to Question 32

32 Have you experienced diarrhea?
   (a) No
   (b) Yes

If No, e-Diary can be submitted.

If Yes, move to Question 33

33 Grade the severity of diarrhea based on the descriptions below:
   (a) 1 (Mild): No interference with activity
   (b) 2 (Moderate): Some interference with activity
   (c) 3 (Severe): Significant, prevents daily activity
   (d) 4 (ER or hospital visit): ER visit or hospitalization

e-Diary can be submitted

For Patients ≥60 years of age ONLY:

1 Have you felt as if you can't think clearly?
   (a) No
   (b) Yes
2 Have you experienced any loss or decrease in your appetite?
   (a) No
   (b) Yes

3 Do you take supplemental oxygen?
   (a) No
   (b) Yes

If No, e-Diary can be submitted.

If Yes, move to Question 4

4 Have you needed to increase your baseline intake?

(a) No

(b) Yes

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug 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
BSSR	blinded sample size re-estimation
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
CV	coefficient of variation
DBL	database lock
DILI	Drug Induced Liver Injury
DNA	deoxyribonucleic acid
DP	drug product
DSMB	Data Safety Monitoring Board
DUS	disease under study
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ELF	epithelial lung fluid
ELISpot	enzyme-linked immune absorbent spot
Fc	fragment crystallizable region
FcγR	Fc gamma receptor(s)
FcRn	neonatal Fc receptor(s)
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
FTIH	first time in human

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HL	Hy's Law
IB	Investigator's Brochure
IATA	International Airline Transportation Association
IC_{80}	80% maximal inhibitory concentration
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
MERS-CoV	Middle East respiratory syndrome coronavirus
nAb	neutralizing antibody
NOAEL	no-observed-adverse-effect level
NOCD	new onset chronic disease
NP	nasopharyngeal
PBMC	peripheral blood mononuclear cell
PHL	Potential Hy's Law
PI	Principal investigator
PK	pharmacokinetic(s)
RBD	receptor binding domain
RNA	ribonucleic acid
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RTSM	Randomization and Trial Supply Management
S	spike

Abbreviation or special term	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
sgmRNA	subgenomic RNA
SoA	Schedule of Activities
$t_{1/2}$	terminal half-life
TBL	total bilirubin level
TCR	tissue cross-reactivity
TM	triple mutation
ULN	upper limit of normal
WOCBP	women of childbearing potential
w/v	weight per volume
YTE	Immunoglobulin constant heavy chain substitution to modify the half-life of the antibody (M252Y/S254T/T256E)

Appendix I Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Version 9.0, 26 July 2021

Key amendment and rationale for change:

In response to health authority feedback, the following changes have been made:

- The primary analysis of the primary endpoint will include all participants who were hospitalized due to COVID-19, regardless of severity. Previously, only participants who were hospitalized due to COVID-19 that met the protocol-defined criteria for severe were included.
- The key supportive analysis of the primary endpoint, in which participants who receive a COVID-19 vaccine or preventive product are censored 14 days following receipt (referred to as "vaccine-efficacy censor" estimand), has been removed.
- A key supportive analysis of the primary endpoint, in which the endpoint is defined as the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP and prior to Day 183, has been added and included in the hierarchical testing strategy.

In addition, an independent Morbidity Adjudication Committee will be constituted to 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. Only adjudicated deaths will be included in efficacy endpoints. 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.

A clarification that all participants who become unblinded to treatment (regardless of the reason) will be considered as intercurrent events rather than only those who became unblinded to consider vaccination for COVID-19.

Synopsis, Sections 3 (Objective and Endpoints), 9.4.1 (General Considerations): Clarification added that all participants who become unblinded to treatment regardless of the reason (rather than only those who became unblinded to consider vaccination for COVID-19) will be considered as intercurrent events.

Synopsis, New Section added Section 9.7 (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.

Section 6.3.3 (Procedures for Unblinding): For clarification purposes, a cross-reference has been added to Section 6.5.1 COVID-19 Vaccines; this section describes how participants can become unblinded on request.

Sections 9.4.1 (General Considerations) and 9.4.2.1 (Primary Endpoint): Primary analysis and primary endpoint have been updated to include all participants who were hospitalized due to COVID-19, regardless of severity.

Section 9.4.5 (Methods for Multiplicity Control): The key supportive analysis, in which participants who receive a COVID-19 vaccine or preventive product are censored 14 days following receipt, has been removed from the hierarchical testing strategy and a key supportive analysis, in which the endpoint is defined as the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP and prior to Day 183, has been added.

Version 8.0, 29 June 2021

Key amendment and rationale for change:

The strategy for handling intercurrent events for the primary efficacy endpoint is to censor participants who become unblinded to treatment assignment to consider vaccination against COVID-19 at the date of unblinding, regardless of whether they subsequently receive a COVID-19 vaccine/preventive product. While the impact of unblinding on the interpretation of the primary endpoint is unknown, receipt of vaccine is expected to affect the interpretation since efficacy of COVID-19 vaccines has been demonstrated. Therefore, an additional estimand strategy, in which the intercurrent event is receipt of a COVID-19 vaccine, has been included as a key supportive analysis of the primary endpoint.

The level of unblinding at the primary analysis will be approximately 30% and is likely to increase as the study continues. Since participants who become unblinded to treatment assignment are censored at the date of unblinding for the key secondary objective to estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366, it is unlikely to yield different results from that of the primary analysis. Therefore, this secondary objective will be changed to an exploratory objective and the endpoint of incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366 removed from the multiple testing hierarchy. Instead, the important secondary objective to estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the

prevention of SARS-CoV-2 infection and endpoint of incidence of participants who have a post-treatment response for SARS-CoV-2 nucleocapsid antibodies will be included in the multiple testing hierarchy.

Synopsis, Section 3 (Objectives and Endpoints): The key secondary objective to estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366 has been removed and replaced with the objective to estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection. The key secondary endpoint of incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366 has been removed and replaced with the endpoint of incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.

Section 4.2.1 (Rationale for Study Endpoints): Rationale for endpoint of incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366 removed. A rationale for key secondary endpoint, for SARS-CoV-2 nucleocapsid antibodies, which has been promoted from the secondary endpoints, has been added. The determination of the post-baseline SARS-CoV-2 nucleocapsid antibody response in study participants will enable the assessment of whether or not AZD7442 prevents asymptomatic infections as well as symptomatic infections.

Section 6.5.1 (COVID-19 Vaccines): Clarification added that participants receiving a COVID-19 vaccine may remain in the study for safety follow-up.

Sections 9.4.1 (General Considerations), 9.4.2.1 (Primary Endpoint), 9.4.5 (Methods for Multiplicity Control): An analysis of the primary endpoint, which censors study participants 14 days following receipt of a COVID-19 vaccine/preventive product, has been included as a key supportive analysis of the primary endpoint and will be included in the multiple testing hierarchy. A period of 14 days from vaccine receipt has been chosen so that the analysis is unlikely to be confounded with vaccine efficacy (Polack et al 2020).

Section 9.4.2.2 (Secondary endpoint(s)): The key secondary endpoint of incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing with IMP through Day 366 has been removed and replaced with the endpoint of incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies and clarification that this will be analyzed at the time of the primary analysis.

Version 7.0, 07 April 2021

Key amendment and rationale for change:

Highly efficacious vaccines against SARS-CoV-2 are being deployed on a mass scale in the participating countries and a higher proportion of participants in the study are electing to become unblinded to consider vaccination for COVID-19 than was originally expected. The process of vaccination has accelerated further in the past 2 to 3 weeks. Consequently, the probability to observe primary endpoint events will diminish with increasing vaccination of the enrolled population. Modelling results suggest that the unblinding rate is increasing over time and that by the time 30% unblinding is reached, the annualized attack rate will have begun to decelerate and will further decline in proportion to the unblinding. This puts the delivery of the study at significant risk. In order to reduce the potential impact of unblinding on the study's ability to robustly quantify placebo-controlled efficacy, the primary analysis has been adjusted to be conducted after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs first. Taking the earlier of these 2 scenarios will avoid an unnecessary delay to reporting trial results irrespective of additional unblinding acceleration. Additionally, the 30-day observation period has been removed as the current pace of unblinding makes this addition untenable. If the unblinding rate does not accelerate beyond the predicted, then the study is likely to observe the 24 primary endpoint events (congruent with the previous version of the protocol).

Synopsis, Sections 1.2 (Schematic), 9.1 (Statistical Hypotheses), 9.4 (Statistical Analyses), 9.4.2.1 (Primary Endpoint), 9.4.5 (Methods for Multiplicity Control): The timing of the primary analysis has been changed from '30 days after the 24th primary endpoint events have occurred' to 'after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs first'.

Synopsis: To correct a mistake in the previous version of the CSP 'participants will undergo follow-up for one year (until Day 366)' has been changed to 'participants will undergo follow-up for 15 months (until Day 457)'.

Section 5.1 (Inclusion Criteria): To correct an inconsistency in the CSP the instructions regarding the pregnancy testing in inclusion criterion 5 have been changed from 'All women of childbearing potential must have a negative serum pregnancy test result at Visit 1 and throughout the study as indicated per the SoA' to 'All women of childbearing potential must have a negative urine pregnancy test result at Visit 1 and throughout the study as indicated per the SoA'.

Version 7.0, 07 April 2021
Synopsis, Section 9.2 (Sample Size Determination): The sample size and power analysis have been updated to account for the event-driven approach for the primary analysis timing. **Section 9.2 (Sample Size Determination):** Moved text discussing the timing of analyses to Section 9.4 (Statistical Analyses). Removed reference to the BSSR. At the time of this protocol amendment the study has completed enrolment with no plans to further adjust the sample size. **Section 9.4.2.2 (Secondary Endpoint(s))**: To correct a mistake in the previous version of the CSP 'the endpoint will be evaluated at the final analysis (ie, through Day 366)' has been changed to 'the endpoint will be evaluated through Day 366. **Appendix A7 (Data Quality Assurance):** Clarification that 'source data review' is being performed and not 'source data verification' as previously stated.

Version 6.0, 18 March 2021
Key amendment and rationale for change: Highly efficacious vaccines against SARS-CoV-2 are being deployed on a mass scale in the participating countries and a higher proportion of participants in the study are electing to become unblinded to consider vaccination for COVID-19 than was originally expected. In order to further reduce the potential impact of unblinding on the study's ability to robustly quantify efficacy, the primary analysis will be conducted 30 days after the 24th primary endpoint event has occurred. This period allows sufficient time for absorption and systemic exposure of AZD7442 administered IM and any other events occurring during this time interval will also be evaluated. Furthermore, to remove recruitment restrictions the stratification caps have been removed from Cohorts 1 and 2. To provide data on AZD7442 for 5 half-lives, the study has been extended to 15 months allowing a safety assessment via a phone call and an optional serum sample for PK, ADA, and nAb to be added at Day 457. Study endpoints have been adjusted accordingly. **Synopsis, Sections 1.2 (Schematic), 3 (Objectives and Endpoints), 4.1 (Overall Design), 6.1.1 (Investigational Medicinal Products), 9.4 (Statistical Analysis), 9.4.3.1 (Primary Endpoint(s)), Table 2 (Schedule of Activities: Treatment and Follow-up Period – Main Study):** To provide safety and PK assessments after 5 half-lives, the study has been

Version 6.0, 18 March 2021

extended from last visit on Day 366 to last visit on Day 457. Endpoints for safety and nAb have been adjusted to reflect this additional time point.

Synopsis, Section 4.1 (Overall Design), 6.3.1 (Randomization): Stratification caps have been removed from Cohorts 1 and 2.

Synopsis, Sections 1.2 (Schematic), 3 (Objectives and Endpoints), 4.2.1 (Rationale for Study Endpoints), 9.1 (Statistical Hypotheses), 9.4.2.1 (Primary Endpoint): The efficacy evaluation period is revised to Day 183, based on anticipated elimination half-life, and allowing for more follow-up time to be included in the primary analysis.

Synopsis, Sections 1.2 (Schematic), 9.1 (Statistical Hypotheses), 9.2 (Sample Size Determination), 9.4 (Statistical Analyses), 9.4.2.1 (Primary Endpoint), 9.4.5 (Methods for Multiplicity Control), 9.5 (Interim Analyses): Per the above rationale, the primary endpoint has been changed from Day 92 with a minimum of 24 primary endpoint events observed to 30 days after the 24th primary endpoint event has occurred.

Section 2.2.2 (Summary of Nonclinical Pharmacokinetics and Drug Metabolism): Safety margins updated from emerging data from Phase I study. Results from cynomolgus monkey GLP toxicology study updated with week 8 data.

Sections 9.4.1 (General Considerations), 9.4.2.1 (Primary Endpoint), 9.4.5 (Methods for Multiplicity Control): A key supportive analysis of the primary endpoint using a treatment policy strategy has been added per regulatory agency feedback.

Corrected typos are not listed above.

Version 5.0, 12 February 2021

Key amendment and rationale for change:

The study had been initially sized to allow for a more detailed assessment of efficacy, including greater precision in subpopulations, and therefore had >95% power to demonstrate that the lower bound of the 2-sided 95% CI for efficacy is greater than 0 (assuming an observed annualized attack rate of 3% in the placebo group and true efficacy of 80%). Highly efficacious vaccines against SARS-CoV-2 are being deployed on a mass scale in the participating countries and a higher proportion of participants in the study are electing to become unblinded to consider vaccination for COVID-19 than was originally expected. In order to reduce the potential impact of unblinding on the study's ability to

Version 5.0, 12 February 2021

robustly quantify efficacy, the primary analysis will be conducted at an earlier time point and the strategy for handling intercurrent events for the primary efficacy endpoint will be changed from a treatment policy strategy to a while on treatment strategy, which was previously a sensitivity analyses. The amended study design will have ~90% power to demonstrate that the lower bound of the 2-sided 95% CI for efficacy is greater than 0 under the same assumptions.

D8850C00002 [PROVENT] is being conducted using AZD7442 material derived from a non-clonal pool of cells from a pooled batch (separately manufactured pools for AZD8895 and AZD1061). Clonal material from a single production cell line that forms a Master Cell bank will be used as the source of the commercial supply. The addition of a subset of participants in PROVENT, to be treated with the clonal material, will provide clinical data on the clonal material in the prophylaxis population.

To incorporate health authority feedback, the protocol has also been amended to include an additional subset of 150 participants, who will receive clonal IMP or placebo in a 2:1 ratio. Based on the availability of clonal material, and to ensure that sufficient data will be available with the clonal material, the sample size has been increased from 5000 to 5150 participants. The clonal material subset will be enrolled in the US.

Synopsis, Figure 1 (Study Design), Sections 3 (Objectives and Endpoints), 4.2.1 (Rationale for Study Endpoints), 9.1 (Statistical Hypotheses), 9.2 (Sample Size Determination), 9.4 (Statistical Analyses), 9.4.1 (General Considerations), 9.4.2.1 (Primary Endpoint), and 9.4.5 (Methods for Multiplicity Control): Per the above rationale, the primary endpoint has been changed from Day 183 to Day 92 with a minimum of 24 primary endpoint events occurred, and the estimated power recalculated to reflect this. Timeframes across the CSP have been updated accordingly. The strategy for handling intercurrent events for the primary and key secondary endpoint has also been changed from 'analyzed regardless' to 'censored at the date of' the intercurrent event.

Synopsis, Sections 4.1 (Overall Design), 9.2 (Sample Size Determination) and Figure 2 (Study Dose Exposure Expansion): Text updated to include an additional 150 US participants who will receive clonal material or placebo in a 2:1 ratio.

Table 2 (Schedule of Activities: Treatment and Follow-up Period – Main Study): In the previous amendment the assignment of some footnotes was incorrect, this mistake has been corrected.

Table 3 (Schedule of Activities: Illness Visits (Participants with Qualifying Clinical Symptoms) and Section 8.6.1.1 (Virologic Assessments): Footnote 'f' and main body text

Version 5.0, 12 February 2021
updated to clarify that both the local and central tests for SARs-CoV-2 RT-PCR should be collected when specified. **Section 6.5 (Concomitant Therapy) and Table 7 (Permitted, Restricted, and Prohibited Medications):** Text updated to specify that any COVID-19 vaccination should be recorded by the investigator. The table has been updated for clarity and to avoid confusion at study sites. Allergy therapy should be allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Visit 1 and there is no anticipated change during the treatment period. The stipulation that commercial biologics, prednisone, or immunosuppressive medications should not be administered on the same day of IMP has been removed. **Section 8.1.1 (Monitoring COVID-19 Symptoms) and Table 2 (Schedule of Activities: Treatment and Follow-up Period – Main Study):** To ensure participants with qualifying COVID-19 symptoms are included in the Illness Visits as soon as possible, additional instructions to enquire about symptoms for the past 7 days have been added to the weekly phone calls. Furthermore, the investigators are instructed that participants with symptoms must be enrolled on Illness Visits within 3 days of those symptoms being identified. **Section 9.4.4 (Pharmacokinetic and Anti-drug Antibody)**: Planned analysis updated to reflect the addition of participants receiving clonal material and the requirement to compare clonal versus pooled data. **Sections 9.5 (Interim Analyses), 9.6 (Data Safety Monitoring Board), and Appendix A5 (Committees Structure):** To accommodate the earlier time point for the primary analysis endpoint (changed from Day 183 to Day 92), the planned futility interim analysis has been removed. No interim analyses are now planned for this study. Corrected typos are not listed above.

Version 4.0, 21 December 2020
Key amendment and rationale for change: Highly efficacious vaccines against SARS-CoV-2 are being deployed on a mass scale. Top priority target populations for vaccine administration include residents of long-term care facilities. These long-term care facility residents are a key target population for this study, with up to 60% of the study population in Cohort 1 to be drawn from them. Given the

Version 4.0, 21 December 2020

extreme vulnerability of this population, and the apparently high efficacy of the vaccines in the elderly, this study should not delay or obstruct vaccine access to those who could benefit from it. Therefore, guidance for SARS-CoV-2 vaccine use has been added to the protocol.

Due to the ongoing unprecedented situation caused by the COVID-19 pandemic, AstraZeneca believes the opportunity to participate in AZD7442 clinical studies should be available to employees and their family members who are not involved in the AZD7442 development program. Therefore, the criterion excluding AstraZeneca employees has been amended to allow those employees and their family members not involved in AZD7442 development to participate in this study, if otherwise eligible. This change aligns this restriction with the exclusion criterion currently used in AstraZeneca's clinical study of its anti-SARS-CoV-2 vaccine, and is therefore consistent with existing precedent.

Participants will be permitted to enter the study if they have previously received immunoglobulins, including mAbs that have been approved for an indication other than COVID-19. AZD7442 and other mAbs will not be co-administered. Monoclonal antibodies approved for indications other than COVID-19 that have been administered prior to consideration for this trial will not disqualify a participant from participation in this study. After randomization, they are permitted at any point during the study other than the day of IMP administration.

Allowing the use of other mAbs during the study does not appear to pose any safety risk. AZD7442's mAbs bind specifically to the receptor binding domain of the Spike protein of SAR-CoV-2, but not to human targets. Published mAb-mAb interaction studies are rare. One clinical study of co-administration of pertuzumab and trastuzumab + docetaxel via separate infusions, which each bind to different epitopes on the HER2 receptor, illustrated that the PK of one mAb is not affected by the administration of the other (Cortés et al 2013). Therefore, it is not expected that the action of AZD7442 will be affected by the presence of another mAb, including its PK parameters, clearance and elimination. Any potential impact on AZD7442 PK will be examined for any participants that have received a commercial mAb.

Synopsis, Sections 3 (Objectives and Endpoints) and 9.4.1 (General Considerations): To account for increased availability of COVID-19 vaccines the definition of intercurrent events was expanded to include, "become unblinded to properly consider vaccination for COVID-19".

Synopsis, Sections 4.1 (Overall Design) and 6.3.1 (Randomization): The imminent deployment of highly effective vaccines against SARS-CoV-2 may severely diminish the study's ability to recruit, as originally planned, from residents of long-term care facilities.

Version 4.0, 21 December 2020

Therefore, the proportions of subjects required from different categories has been changed to be more flexible. The overall recruitment cap for Cohort 1 was changed from 'not exceeding 65%' to 'not exceeding 80%'. Of these, the study will attempt to recruit 30%-60% from residents of long-term care facilities, including skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults For Cohort 2 the overall cap has been increased from 50% to 80%. Of these, the study will attempt to recruit 30%-60% on the basis of being at increased risk of SARS-CoV-2 infection due to location or circumstances that put them at appreciable risk of exposure. The rest of the participants (40%-70%) will be those with chronic medical conditions, or having an immunocompromised state or being vaccine intolerant.

Table 2 (Schedule of Activities: Treatment and Follow-up Period): For clarity, 'Early' has been added to the Discontinuation visit column header.

Table 2 (Schedule of Activities: Treatment and Follow-up Period), Table 3 (Schedule of Activities: Illness Visits), and Section 8.5.2.3 (Assessment of Mucosal Responses): To allow for potential logistical problems caused by the COVID-19 pandemic, text has been added to indicate that nasal adsorption sampling can be missed only if test supplies are not available.

Section 2.3.1 (Risk Assessment): The date of the data cut-off for risk assessment has been changed to 03 November 2020 to reflect the ongoing Study D8850C00001.

Section 5.2 (Exclusion Criteria): Criterion 9 'Receipt of blood products or immunoglobulins, including mAbs, within 6 months, or 5 antibody half-lives if longer than 6 months, prior to screening (see Table 7)' has been deleted per the rationale provided above.

Section 5.2 (Exclusion Criteria): Criterion changed from: '13. Employees of the Sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals' to '12. Employees of the Sponsor involved in planning, executing, supervising, or reviewing the AZD7442 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals'.

Table 7 (Permitted, Restricted, and Prohibited Medications): The instruction that any SARS-CoV-2 or COVID-19 vaccines should not be considered routine vaccines, has been added.

Version 4.0, 21 December 2020
New Section 6.5.1 (COVID-19 Vaccines): New section added to describe the procedures required to allow potential and current study participants to receive a COVID-19 vaccine. **Section 8.1.2 (Severe or Critical Criteria):** Severe COVID-19 definition updated for clarity and to match all AZD7442 studies 'either pneumonia (fever, cough, tachypnea, dyspnea, lung infiltrates)' changed to 'either pneumonia (fever, cough, tachypnea **or** dyspnea, **and** lung infiltrates)'. **Section 8.2.4 (Clinical Safety Laboratory Assessments):** For clarity regarding required laboratory tests, the calculation of eGFR has been added. Corrected typos are not listed above.

Version 3.0, 13 November 2020
Key amendments and rationale for changes: Changes have been made to the protocol in response to health authority comments, which requested the inclusion of increased safety monitoring with particular emphasis on potential hypersensitivity reactions immediately after IMP administration. As of 14 September 2020 no hypersensitivity reactions have been observed in the Phase I study. Health authority comments also recommended considering testing the null hypothesis of no difference between treatment groups without a specific lower bound to demonstrate statistical superiority over placebo. **Title Page:** Updated to include study acronym. **Synopsis, Table 4 (Objectives and Endpoints), Table 11 (Populations for Analysis), Section 9.4.1 (General Consideration):** Addition of a new analysis set, "full pre-exposure analysis set". Replacement of "full analysis set" by "full pre-exposure analysis set", which will be used as the analysis set (population) for the primary estimand to exclude participants with prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, to focus the analysis on the intended pre-exposure population. **Synopsis, Table 2 (Schedule of Activities: Treatment and Follow-up Period), Section 4.1 (Overall Design), and New Section Added 8.2.5.1 (Monitoring After IMP Administration):** Addition of wording to increase safety monitoring, including the addition of a Sentinel Cohort so that the first 15 participants are dosed and observed for 4 hours before further participants are dosed in Stage 1. The remaining Stage 1 participants will

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then undergo safety monitoring for 2 hours post IMP administration. If hypersensitivity reactions are observed during Stage 1, safety monitoring for 2 hours post IMP administration will be implemented for all Stage 2 participants, otherwise the minimum safety monitoring time will be 1 hour. In addition, the Sentinel Cohort will be contacted daily for the first 4 days after IMP administration.

Synopsis, Sections 9.1 (Statistical Hypotheses), and 9.4.2.1 (Primary Endpoint): Removal of "lower bound of 2-sided 95% CI is required to be greater than 30%" constraint from the statistical significance criteria. The null hypothesis testing no difference between AZD7442 and placebo groups is considered sufficient for demonstrating statistical superiority over placebo in a more targeted population.

Synopsis, Figure 1 (Study Design), 9.5 (Interim Analyses): Addition of an interim analysis for futility after the last participant dosed has been followed through Day 92, to ensure a reasonable probability of halting the trial if AZD7442 is ineffective, and a high probability of continuing the trial if AZD7442 is effective.

Synopsis, Section 9.2 (Sample Size Determination): Further details added on the sample size assumptions.

Table 1 (Schedule of Activities: Screening Period): In response to concerns about the ability to receive RT-PCR test results prior to randomization, the protocol has been amended to specify that screening RT-PCR results are not required prior to randomization and dosing. Footnote added to clarify the use of local versus central laboratory results. To align with main body AEs removed.

Table 1 (Schedule of Activities: Screening Period) and Section 5.1 (Inclusion Criteria): Addition of inclusion criterion and modification to schedule of events clarifying that a negative SARS-CoV-2 serology test result is required at screening for inclusion in the study.

Table 2 (Schedule of Activities: Treatment and Follow-up Period) and Section 8.2.5 (Injection Site Inspection): Instructions added to footnote to increase the number of times the injection site is inspected after IMP administration and in the main body a list of assessments to be performed described.

Table 3 (Schedule of Activities: Illness Visits): 'Whole blood' removed from PBMC collection.

Table 3 (Schedule of Activities: Illness Visits), Section 8.1.1 (Monitoring COVID-19 Symptoms), and Section 8.1.3 (Illness Visits): Footnotes added to clarify the use of local

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versus central laboratory results, to allow home visits if necessary, and to specify that the Illness Visit schedule should be completed in addition to the Main Study schedule.

Table 4 (Objectives and Endpoints): Due to operational feasibility 'blood collection' removed for SARS-CoV-2 viral load exploratory endpoint.

Sections 5.1 (Inclusion Criteria): To ensure consistent interpretation of inclusion criterion 2a, definition added for 'Intolerant to Vaccine'.

Sections 5.1 (Inclusion Criteria), 8.1.6 (Illness Diary), 8.3 (Adverse Events and Serious Adverse Events), and Appendix A3 (Informed Consent Process): To avoid possible confusion between differing jurisdictions 'legally authorized representative' was updated to 'legally authorized representative or equivalent representative as locally defined'.

Section 5.2 (Exclusion Criteria): To ensure participants have not been previously exposed to COVID-19, criterion 2 was amended to clarify that participants with a positive SARS-CoV-2 result at the time of screening should be excluded.

Section 5.2 (Exclusion Criteria): Addition of new criterion to exclude participants who lack capacity to provide their own informed consent in jurisdictions where this is not permitted.

Section 6.1.1 (IMP): Text added to clarify that should a participant experience an immediate hypersensitivity reaction after receipt of the first IM injection, the second IM injection should not be given. Instructions for anaphylactic reactions added to Appendix F.

Table 7 (Permitted, Restricted, and Prohibited Medications): Updated to specify that 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.

Section 7.4 (Study Suspension/Early Termination): Section updated to include stopping rules which will be implemented should a grade IV or SAE hypersensitivity reaction occur. Furthermore, the study will be paused should a grade III hypersensitivity or a grade III injection site reaction(s) occur within the first 300 participants. Due to the age and comorbidity profile of the study population, the grade III hypersensitivity/injection site reaction stopping rules are limited to the first 300 participants, this is to reduce the likelihood of unrelated events temporarily stopping the study.

Section 8.1.1 (Monitoring COVID-19 Symptoms) and 8.3.6 (Adverse Events Based on Signs and Symptoms): Clarified that symptoms of COVID-19, confirmed SARS-CoV-2

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infection, and/or diagnosis of COVID-19 will be collected and recorded in the eCRF as an AE. **Section 8.1.2 (Severe or Critical Criteria):** Modified to correctly correspond with severe or critical criteria for COVID-19 based on pneumonia or hypoxemia parameters and the WHO clinical progression scale. WHO clinical progression scale updated to the recently published 10-point guideline. **Section 8.1.6 (Illness e-Diary) and New Appendix G (e-Diary):** To allow for version control the e-Diary has been added to the appendices. **Section 8.2.4.1 (Females Only):** Footnotes added to clarify pregnancy and FSH testing. **Section 8.3.2 (Follow-up of AEs and SAEs) and Appendix B2 (Definition of Serious Adverse Event):** Severity ratings adjusted to align with CTCAE event grading. **Section 8.3.4 (Adverse Events of Special Interest) and New Appendix Added Appendix F (Anaphylaxis):** Appendix F added to describe definition and management of anaphylaxis and other hypersensitivity/administration reactions. Injection site reaction(s) added as an AESI. **Section 8.6.1.1 (Virologic Assessments):** IL-D14 added to text to match schedule of activities. **Section 9.6 (Data Safety Monitoring Board), Appendix A5 (Committees Structure):** Text added to clarify the frequency of the data review meeting, pre-specified futility analysis, and to confirm that there is no formal efficacy look by the DSMB with the potential for early stopping due to efficacy planned for this study. Added criteria for pausing the study for DSMB review to ensure safety oversight (ie, halting the trial if AZD7442 is harmful).

Version 2.0, 26 October 2020
Key amendments and rationale for changes: **Synopsis and Section 4.1 (Overall Design), and Section 7.4 (Study Suspension/Early Termination):** Addition of wording that if the study is suspended or the decision is made

not to proceed from Stage 1 to Stage 2, a protocol amendment will be submitted to Health Authorities. **Section 5.1 (Inclusion Criteria), Inclusion Criterion 2:** Expansion of the criterion to clarify definition of participants who are in an immunocompromised state to include those with solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines.

Version 1.0, 07 October 2020
Initial creation

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