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**Clinical Study Protocol**

Study Intervention AZD7442  
Study Code D8851C00001  
Version 7.0  
Date 30 June 2021

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**A Phase III Randomized, Double-blind, Placebo-controlled,  
Multicenter Study to Determine the Safety and Efficacy of  
AZD7442 for the Treatment of COVID-19 in Non-hospitalized  
Adults**

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**Regulatory Agency Identifier Number(s):** EudraCT Number: 2020-005315-44  
IND 150712

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:** D8851C00001

**Amendment Number:** Amendment 6

**Study Intervention:** AZD7442, a combination product of 2 monoclonal antibodies (AZD8895 and AZD1061)

**Study Phase:** Phase III

**Short Title:** Phase III Double-blind, Placebo-controlled Study of AZD7442 for Treatment of COVID-19 in Outpatient Adults

**Acronym:** TACKLE (Treating acute COVID-19 condition with a long half-life engineered antibody)

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

**International Co-ordinating Investigator:** Prof Hugh Montgomery, University College London, UK

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Version 7.0 [Amendment 6]	30 June 2021
Version 6.0 [Amendment 5]	21 April 2021
Version 5.0 [Amendment 4]	31 March 2021
Version 4.0 [Amendment 3]	10 March 2021
Version 3.0 [Amendment 2]	26 February 2021
Version 2.0 [Amendment 1]	22 December 2020
Original Protocol	11 December 2020

### Version 7.0, 30 June 2021

Key amendments and rationale for changes:

Due to regional differences in medical practice for COVID-19, the primary analysis population has been clarified to ensure that the efficacy of AZD7442 for the treatment of COVID-19 is assessed only in non-hospitalized adults.

The study was initially powered at 95%, however to ensure a timely assessment of efficacy during the pandemic, statistical power has been reduced to 90%. As a result, the number of events required for the primary analysis has been reduced. Statistical power of at least 90% is considered sufficient for Phase III studies.

Published data from non-hospitalized COVID-19 patients showed that most COVID-19-related hospitalizations or deaths occur disproportionately within the first two weeks of drug administration (Weinreich et al 2021). As the Poisson regression model assumes a constant hazard over time, it is therefore likely that the data do not fit a Poisson distribution. Consequently, the primary analysis method has been amended to the Cochran-Mantel-Haenszel (CMH) approach, consistent with methods used in other studies.

Alternative estimands for the primary efficacy population have been added to assess efficacy in clinically important subpopulations identified in recently published data (Weinreich et al 2021). These supportive estimands will be included in the multiple testing hierarchy. The 3 new analysis sets (subpopulations) are defined as follows:

Modified full analysis set	All participants in the full analysis set who received IMP $\leq 7$ days from symptom onset and were not hospitalized at
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	baseline ( $\leq$ Day 1) for isolation purposes.
Early intervention analysis set	All participants in the modified full analysis set who received IMP $\leq$ 5 days from symptom onset.
Seronegative analysis set	All participants in the modified full analysis set who were seronegative at baseline.

**Synopsis, Sections 1.2 (Schema), 4.1 (Study Design), 9.1 (Statistical Hypotheses), 9.4.1 (General Considerations):** The number of primary endpoint events required for the primary analysis has been reduced from 52 to 43 and this will be sufficient to provide 90% power for the primary analysis. The data cut-off for the primary analysis will be 30 days after approximately 43 primary endpoint events have been confirmed in the primary analysis population. Enrollment will stop when approximately 43 primary events have been confirmed in the primary analysis population.

**Synopsis, Section 9.2 (Sample Size Determination):** Statistical power has been reduced from 95% to 90%, resulting in the number of events required for the primary analysis being reduced from 52 to 43.

**Section 9.3 (Populations for Analysis):** Analysis populations have been defined to accommodate the clarification of the primary endpoint population and the inclusion of additional supportive estimands.

**Section 9.4.1 (General Considerations):** The data cut off has been changed to reflect the change in sample size from 52 to 43 primary endpoint events in the primary analysis population.

**Section 9.4.2.1 (Primary Endpoint):** Primary analysis method has been changed from Poisson regression model to CMH method. Additional supportive estimands have been included in the multiple testing hierarchy.

**Section 9.4.2.2 (Secondary Endpoint):** Analysis population for secondary endpoint has been changed in line with the clarification of the primary analysis population.

**Section 9.4.5 (Methods for Multiple Testing Control):** Additional supportive estimands have been included in the multiple testing hierarchy.

**Section 9.4.6 (Sensitivity Analyses):** Clarification has been added to the analysis method in line with the change to the primary analysis method.

Previous amendments are summarized in Appendix I.

## TABLE OF CONTENTS

TITLE PAGE.....	1
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE.....	3
TABLE OF CONTENTS .....	6
1        PROTOCOL SUMMARY .....	10
1.1     Synopsis.....	10
1.2     Schema.....	15
1.3     Schedule of Activities.....	16
2        INTRODUCTION .....	25
2.1     Study Rationale.....	25
2.2     Background.....	26
2.3     Benefit/Risk Assessment .....	26
2.3.1    Risk Assessment .....	26
2.3.2    Benefit Assessment.....	27
2.3.3    Overall Benefit:Risk Conclusion.....	27
3        OBJECTIVES AND ENDPOINTS .....	27
4        STUDY DESIGN .....	30
4.1     Overall Design .....	30
4.2     CCI	32
4.3     CCI	34
4.4     End of Study Definition.....	35
5        STUDY POPULATION.....	35
5.1     Inclusion Criteria .....	35
5.2     Exclusion Criteria .....	38
5.3     Lifestyle Considerations .....	40
5.4     Screen Failures .....	40
6        STUDY INTERVENTION .....	40
6.1     Investigational Medicinal Products Administered .....	40
6.1.1    Investigational Medicinal Products .....	40
6.2     Preparation/Handling/Storage/Accountability.....	41
6.2.1    Dose Preparation and Administration Instructions.....	42
6.3     Measures to Minimize Bias: Randomization and Blinding.....	42
6.3.1    Randomization.....	42
6.3.2    Blinding .....	42
6.3.3    Procedures for Unblinding.....	43
6.4     Investigational Medicinal Product Compliance .....	43
6.5     Concomitant Therapy .....	43
6.5.1    COVID-19 Vaccination.....	45

6.6	Dose Modification .....	46
6.7	Intervention After the End of the Study .....	46
7	DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL .....	47
7.1	Discontinuation of Investigational Medicinal Product.....	47
7.2	Participant Withdrawal from the Study .....	47
7.3	Lost to Follow-up .....	47
7.4	Study Suspension/Early Termination .....	48
8	STUDY ASSESSMENTS AND PROCEDURES .....	49
8.1	Efficacy Assessments .....	49
8.1.1	Clinical Assessments .....	49
8.1.2	Collect/Update Secondary Contacts .....	50
8.1.3	Survival Status Check.....	50
8.1.4	Participant-reported Symptom Diary.....	50
8.1.5	Return to Usual Health .....	52
8.1.6	<b>CCI</b> [REDACTED]	52
8.1.7	Virologic Studies .....	52
8.2	Safety Assessments.....	52
8.2.1	Physical Examinations.....	52
8.2.2	Vital Signs .....	53
8.2.3	Electrocardiograms .....	53
8.2.4	Clinical Safety Laboratory Assessments .....	53
8.2.4.1	Females Only .....	55
8.2.5	Injection Site Inspection .....	55
8.2.5.1	Monitoring After IMP Administration.....	55
8.3	Adverse Events and Serious Adverse Events .....	56
8.3.1	Time Period and Frequency for Collecting AE and SAE Information.....	56
8.3.2	Follow-up of AEs and SAEs .....	56
8.3.3	Causality Collection .....	58
8.3.4	Adverse Events of Special Interest.....	58
8.3.5	Adverse Events Based on Signs and Symptoms .....	59
8.3.6	Adverse Events Based on Examinations and Tests .....	59
8.3.7	Hy's Law .....	59
8.3.8	Disease Under Study .....	60
8.3.9	Reporting of Serious Adverse Events.....	60
8.3.10	Pregnancy .....	61
8.3.10.1	Maternal Exposure.....	61
8.3.10.2	Paternal Exposure .....	62
8.3.11	Medication Error.....	62
8.4	Overdose .....	62
8.5	Human Biological Samples .....	63
8.5.1	Pharmacokinetics Assessments .....	63
8.5.1.1	Determination of Drug Concentration .....	64

8.5.2	<b>CCI</b>	64
8.5.2.1	Anti-drug Antibody.....	64
8.5.2.2	SARS-CoV-2 Serology.....	64
8.5.2.3	<b>CCI</b>	65
8.5.2.4	<b>CCI</b>	65
8.5.2.5	<b>CCI</b>	65
8.5.3	<b>CCI</b>	65
8.5.3.1	<b>CCI</b>	65
8.6	Human Biological Sample Biomarkers .....	66
8.6.1	Collection of Mandatory Samples for Biomarker Analysis .....	66
8.6.1.1	<b>CCI</b>	66
8.7	Medical Resource Utilization and Health Economics .....	66
9	STATISTICAL CONSIDERATIONS .....	66
9.1	Statistical Hypotheses.....	66
9.2	Sample Size Determination .....	67
9.3	Populations for Analyses .....	67
9.4	Statistical Analyses.....	68
9.4.1	<b>CCI</b>	69
9.4.2	Efficacy.....	69
9.4.2.1	Primary Endpoint(s) .....	69
9.4.2.2	Secondary Endpoint(s) .....	71
9.4.2.3	<b>CCI</b>	73
9.4.3	Safety .....	73
9.4.3.1	Primary Endpoint(s) .....	73
9.4.3.2	Other Safety Endpoint(s) .....	73
9.4.4	<b>CCI</b>	73
9.4.4.1	<b>CCI</b>	73
9.4.4.2	<b>CCI</b>	74
9.4.5	<b>CCI</b>	74
9.4.6	<b>CCI</b>	74
9.4.7	Subgroup Analyses .....	74
9.5	Interim Analysis .....	75
9.6	Data Safety Monitoring Board .....	75
10	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS.....	75
11	REFERENCES .....	114

## LIST OF FIGURES

Figure 1	Study Design .....	15
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## LIST OF TABLES

Table 1	Schedule of Activities for Cohort 1 .....	16
Table 2	Schedule of Activities for Cohort 2 .....	21
Table 3	Objectives and Endpoints.....	27
Table 4	CCI	41
Table 5	Summary of Permitted, Prohibited, or Restricted Medications .....	44
Table 6	Injection Site Inspection on Day 1 .....	55
Table 7	Populations for Analysis .....	67

## LIST OF APPENDICES

<b>Appendix A</b>	Regulatory, Ethical, and Study Oversight Considerations.....	76
<b>Appendix B</b>	Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting .....	82
<b>Appendix C</b>	Handling of Human Biological Samples.....	87
<b>Appendix D</b>	Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law .....	89
<b>Appendix E</b>	Abbreviations .....	95
<b>Appendix F</b>	WHO Clinical Progression Scale for COVID-19 .....	98
<b>Appendix G</b>	Participant-reported Symptom Diary .....	99
<b>Appendix H</b>	Hospitalization Definition.....	105
<b>Appendix I</b>	Amendment History .....	106

## 1 PROTOCOL SUMMARY

### 1.1 Synopsis

**Protocol Title:** A Phase III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Safety and Efficacy of AZD7442 for the Treatment of COVID-19 in Non-hospitalized Adults

**Short Title:** Phase III Double-blind, Placebo-controlled Study of AZD7442 for Treatment of COVID-19 in Outpatient Adults

**Rationale:** There is an urgent need to rapidly evaluate treatments in the non-hospitalized setting to prevent disease progression and reduce serious complications of COVID-19 and transmission. This Phase III study will assess whether AZD7442 (a combination of 2 mAbs) can safely treat outpatient adults with COVID-19 and prevent either severe COVID-19 or death.

### Objectives and Endpoints

Objective	Estimand Description/Endpoint
<b>Primary</b>	
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either severe COVID-19 or death from any cause through study Day 29.	<p><b>Population:</b> Modified full analysis set</p> <p><b>Endpoint:</b> A composite of either severe COVID-19 or death from any cause through Day 29.</p> <p>Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (<math>\text{SpO}_2 &lt; 90\%</math> in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Appendix F).</p> <p><b>Intercurrent events:</b> The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product prior to Day 29 without already having met the primary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.</p> <p><b>Summary measure:</b> Relative risk reduction of severe COVID-19 or death from any cause in participants taking AZD7442 compared to those taking placebo during the 28-day post-dose period (Day 1 to Day 29).</p>
To evaluate safety and tolerability of a single IM dose of AZD7442 compared to placebo.	AEs, SAEs, and AESIs through end of study.

<b>Key Secondary</b>	
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either death or hospitalization <sup>a</sup> for COVID-19 complications or sequelae through Day 169.	<p><b>Population:</b> Modified full analysis set.</p> <p><b>Endpoint:</b> A composite of either death from any cause or hospitalization<sup>a</sup> for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169).</p> <p><b>Intercurrent events:</b> The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product or becoming unblinded to properly consider vaccination for COVID-19 prior to Day 169 without already having met the key secondary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.</p>
<b>Other Secondary</b>	
To determine if AZD7442 will prevent respiratory failure through study Day 29.	The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen delivery (an oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60 liters per minute, as defined in Sharma et al 2020 and Ashraf-Kashani and Kumar 2017).
To determine whether AZD7442 reduces participants' severity of participant-reported COVID-19 symptoms through Day 29.	COVID-19 symptom severity assessments based on symptom severity scores over time during the 28-day period from and including the day of the dose of AZD7442 or placebo. Each symptom is scored from 0 to 4.
To determine if AZD7442 reduces the progression of participant-reported COVID-19-associated symptoms through Day 29.	Progression through Day 29 of one or more COVID-19-associated symptoms to a worse status than recorded in the participant-reported symptom diary at study entry, prior to start of AZD7442 or placebo.
To determine if AZD7442 reduces SARS-CoV-2 detection or levels of RNA in nasal swabs through Day 29.	Detection (detectable versus undetectable), level, and change from baseline of SARS-CoV-2 RNA from nasal swabs through Day 29.
To evaluate differences in symptom duration between the AZD7442 and placebo treatment groups through Day 29.	<ul style="list-style-type: none"> <li>• Time to return to usual (pre-COVID-19) health through Day 29.</li> <li>• Duration of fever through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater than 37.8°C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken.</li> </ul>
To evaluate the single-dose PK of AZD7442.	Serum concentration and PK parameters.
To evaluate the ADA responses to AZD7442 in serum.	Incidence of ADA to AZD7442 in serum over time.

<sup>a</sup> Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic. See also Appendix H for further guidance on the definition of hospitalization.

ADA Anti-drug-antibody; AE Adverse event; AESI Adverse event of special interest; AUC Area under the plasma concentration-time curve; COVID-19, Coronavirus disease 2019; ECMO Extracorporeal membrane oxygenation; IM Intramuscular; IMP Investigational medicinal product; PK Pharmacokinetic; RNA Ribonucleic acid; SAE Serious adverse event; SARS-CoV-2 Severe acute respiratory syndrome-coronavirus-2; SpO<sub>2</sub> Oxygen saturation; WHO World Health Organization.

CCI

## Overall Design

This is a Phase III, randomized, double-blind, placebo-controlled, multicountry, multicenter study assessing the safety and efficacy of a single 600 mg dose of AZD7442 compared to placebo for the treatment of COVID-19. AZD7442 is a combination product of 2 monoclonal antibodies (AZD8895 and AZD1061), administered as 2 separate IM injections of 300 mg each. All participants will receive background local standard of care therapy (according to participating institution/hospital) regardless of the study treatment group to which they are randomized. Approximately 130 to 140 sites will participate in this study.

Participants will be outpatient adults ( $\geq 18$  years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected  $\leq 3$  days prior to study entry and with  $\leq 7$  days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1.

At least 60% of participants will meet the protocol definition of being at high-risk of progression to severe COVID-19 as defined by any of the following:

- Persons aged 65 years and older at randomization
- Persons aged  $< 65$  years and having at least one of the following conditions:
  - Cancer
  - Chronic lung disease or moderate to severe asthma
  - Obesity (BMI  $> 30$ ; may be based on self-report of recent height and weight measurement)
  - Hypertension
  - Cardiovascular disease (including history of stroke)
  - Diabetes
  - Chronic kidney disease
  - 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

- Sickle cell disease
- Smoking (current or former)

Randomization will be stratified (using centralized blocked randomization) by:

- 1 Time from symptom onset ( $\leq$  5 days versus  $>$  5 days)
- 2 High-risk versus low-risk of progression to severe COVID-19 (high-risk is defined above)

The enrollment of low-risk participants has stopped.

Up to approximately 1700 participants will be randomized in a 1:1 ratio to receive a single IM dose of 600 mg of AZD7442 (n = up to approximately 850) or placebo (n = up to approximately 850) on Day 1. The first 20 participants to be dosed (approximately 10 allocated to the AZD7442 group and 10 allocated to placebo) will form a sentinel group. After the entire sentinel group has been dosed, further enrollment will pause until the sentinel group's safety data through Day 8 has been reviewed by the DSMB in order to provide a recommendation to continue or to halt dosing of additional participants.

Participants will be enrolled into one of 2 independent cohorts:

- Cohort 1 (n = approximately 300), which will include the sentinel group, will undergo more intensive testing to characterize their virological and immunological status, and to correlate that status with clinical outcomes.
- Cohort 2 (n = up to approximately 1400) will be followed for clinical outcomes.

Following screening, and no more than 7 days ('Day 1' symptom count starts from the first day of symptoms) from self-reported onset of COVID-19-related symptoms or measured fever, participants will receive a single dose of IMP. The dose will be administered as 2 separate IM injections (one for AZD8895 and one for AZD1061; the 2 compounds will not be co-administered) in the gluteal region. In Cohort 1, the first 20 participants dosed (ie, the sentinel group) will undergo safety monitoring for 4 hours post IMP administration before further participants are dosed. At each site, there will be an interval of 24 hours after dosing of the first participant in the sentinel group before the next participant can be dosed. The next 80 participants (21 to 100) will then undergo safety monitoring for 2 hours post IMP administration. If hypersensitivity reactions are observed in the first 100 participants, subsequent participants will continue to be monitored for 2 hours post IMP administration, otherwise the minimum safety monitoring time will be 1 hour. In addition, the sentinel group will be contacted daily (in-person or by telephone) for the first 4 days after IMP administration. The study will be temporarily suspended if the criteria listed in Section 7.4 are met. All sites will have access to emergency kits for treatment of severe anaphylactic

reactions/shock and to medical staff trained in using these emergency kits.

After administration of the dose of study intervention on Day 1, participants will undergo 28 days of intensive follow-up, followed by limited follow-up through Day 457.

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

**Number of Participants:** CRM 7 Enrollment of up to approximately 1700 participants is planned, contingent upon safety. At least 60% of participants will meet the protocol definition of being at high-risk of progression to severe COVID-19. Enrollment will stop when approximately 43 primary endpoint events have been confirmed in the primary analysis population.

**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”, unless otherwise specified by the protocol.

**Intervention Groups and Duration:** Participants will be randomized in a 1:1 ratio to receive a single 600 mg dose of AZD7442 or placebo. Investigational medicinal product will be administered on Day 1, and participants will be monitored for up to 15 months after IMP administration.

**Data Safety Monitoring Board:** Yes

### **Statistical Methods**

**Primary Endpoint:** The primary efficacy endpoint is a composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia ( $\text{SpO}_2 < 90\%$  in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Appendix F).

**Sample Size:** Up to approximately 1700 participants will be randomized in a 1:1 ratio to receive a single 600 mg IM dose of AZD7442 ( $n =$  up to approximately 850) or placebo ( $n =$  up to approximately 850) on Day 1.

The study has **CCI** to detect a RRR of **CCI** in the incidence of severe COVID-19/death in the AZD7442 group compared to the placebo group, **CCI**.

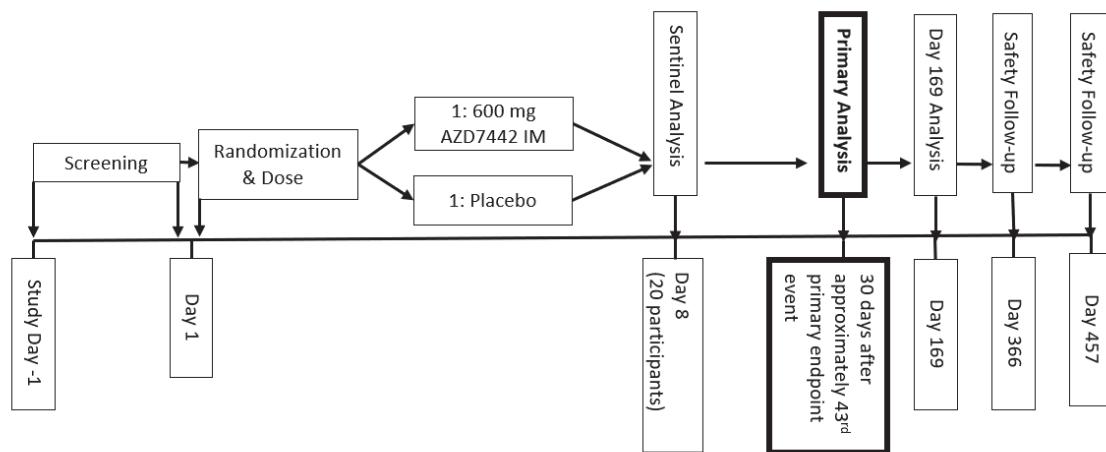
All participants will remain in the study for up to 456 days following the administration of

IMP. The primary analysis will be conducted 30 days after approximately 43 primary endpoint events have been confirmed in the primary analysis population. A Day 169 analysis will be conducted when all participants have been followed through Day 169. A final analysis will be conducted when all participants have completed the study (ie, all participants have completed Day 457 visit, see Figure 1).

The study will be completely double-blind until the primary analysis (ie, blind for participants, Investigators/site staff, and Sponsor/designated clinical research organization). The site personnel, participants, and the study team members who participate in the advice or decisions involving study conduct or day-to-day interactions with the site, will remain blinded until the end of the study (ie, all participants have completed Day 457 visit) to ensure the trial integrity is maintained.

## 1.2 Schema

**Figure 1** Study Design



An independent DSMB will monitor safety throughout, including the safety data through Day 8 from the participants in the sentinel group.  
Primary analysis will be conducted 30 days after approximately 43 events have been confirmed in the primary analysis population.

DSMB Data Safety Monitoring Board; IM Intramuscular

### 1.3 Schedule of Activities

The SoA for Cohort 1 is in Table 1 and the SoA for Cohort 2 is in Table 2.

**Table 1 Schedule of Activities for Cohort 1**

Procedure	Screening Day -1 or Day 1	Treatment and Follow-up Period										Early Discontinuation Visit	Details in Section of CSP
		Day 1	Day 3	Day 6	Day 8	Day 15	Day 29	Day 85	Day 169	Day 366	Day 457		
Window (days)	NA	± 1	± 1	± 1	± 1	± 2	± 4	± 7	± 7	± 7	± 7		
P = In-Person Visit H = Home Visit R = Remote Visit	P	P	P/H <sup>a</sup>	R	P/H <sup>a</sup>	P	P	P	P	P	P/R	P	P
Informed consent	X												
Assignment SID number	X												
Documentation of SARS-CoV-2 infection	X												
Respiratory sample for rapid SARS-CoV-2	X <sup>b</sup>												
COVID-19 Symptom screen	X												5.1
Medical/medication history	X												
Risk categorization	X												4.1
Smoking status	X												
Clinical assessments	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1
Complete physical examination <sup>d</sup>	X										X	X	8.2.1
Targeted physical examination	X	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>	X	X	X	X	X			8.2.1
Vital signs	X	X <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	8.2.2
TriPLICATE 12-lead ECG	X										X	X	8.2.3

**Table 1**  
**Schedule of Activities for Cohort 1**

Procedure	Screening	Treatment and Follow-up Period										Early Discontinuation Visit	Details in Section of CSP	
		Day -1 or Day 1	Day 1	Day 3	Day 6	Day 8	Day 15	Day 29	Day 85	Day 169	Day 366	Day 457		
<b>Window (days)</b>		NA	± 1	± 1	± 1	± 2	± 4	± 7	± 7	± 7	± 7	± 7		
<b>P = In-Person Visit</b> <b>H = Home Visit</b> <b>R = Remote Visit</b>		P	P	P/H <sup>a</sup>	P/H <sup>a</sup>	R	P/H <sup>a</sup>	P	P	P	P/R	P	P	
Hematology		X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X <sup>b,g</sup>	X	8.2.4
Serum chemistry panel		X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X	8.2.4
Serum sample for vitamin D <sup>e</sup>		X <sup>f</sup>												8.5.2.5
Serum sample for zinc <sup>o</sup>		X <sup>f</sup>												8.5.2.5
Urinalysis		X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X	8.2.4
Pregnancy testing <sup>i</sup>		X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X <sup>th</sup>	X	8.2.4.1
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	6.5
Collect/update secondary contacts		X	X	X	X	X	X	X	X	X	X	X		8.1.2
Verify eligibility criteria		X	X											5.1, 5.2
Randomization		X												6.3.1
Survival status check			X	X	X	X	X	X	X	X	X	X	X	8.1.3
Participant-reported symptom diary <sup>j</sup>														8.1.4
Participant-reported symptom reminder <sup>k</sup>														8.1.4
Staff review of participant-reported symptom diary					X	X		X	X	X		X		8.1.4
Retrieval of participant-reported symptom diary											X <sup>l</sup>		X	8.1.4

**Table 1**  
**Schedule of Activities for Cohort 1**

Procedure	Screening		Treatment and Follow-up Period						Early Discontinuation Visit	Details in Section of CSP			
	Day -1 or Day 1	Day 1	Day 3	Day 6	Day 8	Day 15	Day 29	Day 85	Day 169	Day 366	Day 457		
<b>Window (days)</b>		NA	± 1	± 1	± 1	± 2	± 4	± 7	± 7	± 7	± 7		
<b>P = In-Person Visit</b> <b>H = Home Visit</b> <b>R = Remote Visit</b>	P	P	P/H <sup>a</sup>	P/H <sup>a</sup>	R	P/H <sup>a</sup>	P	P	P	P/R	P	P	
Return to usual (pre-COVID-19) health		X	X	X	X	X	X	X	X	X	X	X	8.1.5
Household infection report		X					X	X	X	X	X	X	8.1.6
Study staff-collected mid-turbinate nasal swab for SARS-CoV-2 RT-PCR and sequencing <sup>m</sup>	X <sup>f</sup>	X	X		X	X					X	X	8.1.7
<b>CCI</b>	<b>CCI</b>												
Serum for SARS-CoV-2 serology	X <sup>n</sup>	X	X		X	X	X	X	X	X	X	X	8.5.2.2
<b>CCI</b>	<b>CCI</b>												
Serum for AZD7442 pharmacokinetics		X <sup>n</sup>	X	X		X	X	X	X	X	X	X	8.5.1
Serum for AZD7442 anti-drug antibodies		X <sup>f</sup>					X	X	X	X	[optional]	X	8.5.2.1
<b>CCI</b>	<b>CCI</b>												
<b>CCI</b>	<b>CCI</b>												

**Table 1**  
**Schedule of Activities for Cohort 1**

Procedure	Screening	Treatment and Follow-up Period								Early Discontinuation Visit	Details in Section of CSP		
		Day -1 or Day 1	Day 1	Day 3	Day 6	Day 8	Day 15	Day 29	Day 85	Day 169	Day 366		
<b>Window (days)</b>		NA	± 1	± 1	± 1	± 1	± 2	± 4	± 7	± 7	± 7		
<b>P = In-Person Visit</b> <b>H = Home Visit</b> <b>R = Remote Visit</b>		P	P	P/H <sup>a</sup>	P/H <sup>a</sup>	R	P/H <sup>a</sup>	P	P	P/R	P	P	
<b>CC1</b>													
<b>IMP administration</b>		X										6	
Check injection sites		X <sup>b</sup>	X		X <sup>q</sup>							8.2.5	
Adverse events		X	X	X	X	X	X	X	X	X	X	8.3	
SAEs and AESIs		X	X	X	X	X	X	X	X	X	X	8.3	
Telephone contact for safety monitoring <sup>c</sup>					Daily							8.3.4	
												8.2.5.1	

<sup>a</sup> Visits noted P/H can be performed either in-person at a clinical site or at home depending on the participant's clinical status, availability of safe transfer to sites (eg, to avoid risk of infection spread), and local guidelines for travel restrictions/social distancing. For home visits, a nurse or HCP trained on study procedures will visit the participant at home; nasal swabs, blood collection (where at-home collection is possible), and inspection of injection sites will be performed by the nurse or HCP. Nurse or HCP will ensure shipment of specimens collected and reporting of AEs to study sites.

<sup>b</sup> Perform if no documentation of SARS-CoV-2 infection available.

<sup>c</sup> Assessment will be performed only for participants attending in-person visits, or if a nurse or HCP visiting the participant at home is properly trained for these assessments. Height is recorded only at the screening visit.

<sup>d</sup> Perform pre-dose and 15 minutes ( $\pm$  5 minutes) after both injections are complete.

<sup>e</sup> Perform pre-dose on Day 1.

<sup>f</sup> Hematology panel includes coagulation markers.

<sup>g</sup> Urine pregnancy test (local laboratory) at screening. Perform another urine test (local laboratory) on Day 1 if screening urine test was performed on Day -1. Single serum (central laboratory) must be performed on Day 1. Sample urine test must return negative result before dosing.

<sup>i</sup> Urine pregnancy test (local laboratory).

<sup>j</sup> Participants will report COVID-19-related symptoms daily in an electronic device, starting pre-dose and post-dose on Day 1.

- k Participant will be reminded every day through Day 29 to complete their diary. This reminder will be received through the electronic device.
  - l If Day 29 visit is conducted earlier in  $\pm$  4 day window, participant should retain symptom diary in order to complete required daily entries through Study Day 29.
  - m Mid-turbinate nasal swab is tested centrally. Sequencing applies to nasal swabs collected through Day 15.
  - n Pre-dose sample and post-dose sample (ie, samples obtained prior to and upon completion of IMP administered via IM injections on Day 1).
  - o Serum vitamin D, serum zinc, [CC1] dependent on availability of laboratory kits.
  - p Perform 30 minutes ( $\pm$  10 minutes) after the IMP has been administered and just prior to release from the study site or departure of the study staff.
  - q If evidence of injection site reaction persists at the Day 6 visit, the injection site will be rechecked at each visit until no evidence of an active reaction remains.
  - r The first 20 participants dosed (ie, the sentinel group) will undergo safety monitoring for 4 hours post IMP administration before further participants are dosed. At each site, there will be an interval of 24 hours after dosing of the first participant in the sentinel group before the next participant can be dosed. The next 80 participants (21 to 100) will then undergo safety monitoring for 2 hours post IMP administration. If hypersensitivity reactions are observed in the first 100 participants, subsequent participants will continue to be monitored for 2 hours post IMP administration, otherwise the minimum safety monitoring time will be 1 hour. In addition, the sentinel group will be contacted daily (in-person or by telephone) for the first 4 days after IMP administration. Contact will be made by telephone on days when there is not an in-person visit.
  - s At Day 457 AE/SAE/AESI assessment will be made by telephone only.
    - Note: Remote (denoted by R) visit: either a phone call, or a web-based virtual assessment.
    - Note: Day 6 and Day 8 assessments must be performed on different days.
- AESI Adverse events of special interest; COVID-19 Coronavirus disease 2019; CSP Clinical Study Protocol; ECG Electrocardiogram; HCP Healthcare personnel; IM Intramuscular; IMP Investigational medicinal product; NA Not applicable; Nab Neutralizing antibody; NP Nasopharyngeal; [CC1] RNA RT-PCR Reverse transcription polymerase chain reaction; SAE Serious adverse event; SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2; SID Subject identification number.

**Table 2**  
**Schedule of Activities for Cohort 2**

Procedure	Screening		Treatment and Follow-up Period						Early Discontinuation Visit	Details in Section of CSP	
	Day -1 or Day 1	Day 1	Day 6	Day 8	Day 29	Day 85	Day 169	Day 366	Day 457	Before Day 29	After Day 29
<b>Window (days)</b>		NA	± 1	± 1	± 4	± 7	± 7	± 7	± 7		
<b>P = In-Person Visit</b> <b>H = Home Visit</b> <b>R = Remote Visit</b>	P	P	P/H <sup>a</sup>	R	P	P	P	P	P/R	P	P
Informed consent	X										
Assignment SID number	X										
Documentation of SARS-CoV-2 infection	X										
Respiratory sample for rapid SARS-CoV-2	X <sup>b</sup>										
COVID-19 Symptom screen	X										
Medical/medication history	X										
Risk categorization	X										
Smoking status <sup>c</sup>	X										
Clinical assessments	X	X	X	X	X	X	X	X	X	X	8.1.1
Complete physical examination <sup>d</sup>	X						X	X	X	X	8.2.1
Targeted physical examination	X	X	X <sup>e</sup>	X	X	X	X	X			8.2.1
Vital signs	X	X <sup>e</sup>	X	X	X	X	X	X	X	X	8.2.2
TriPLICATE 12-lead ECG	X				X		X		X	X	8.2.3
Hematology	X <sup>f,g</sup>	X <sup>g</sup>					X	X	X <sup>g</sup>	X	8.2.4
Serum chemistry panel	X <sup>f</sup>	X			X	X	X	X	X	X	8.2.4
Serum sample for vitamin D <sup>h</sup>	X <sup>f</sup>										8.5.2.5
Serum sample for zinc <sup>i</sup>	X <sup>f</sup>	X			X	X	X	X	X	X	8.5.2.5
Urinalysis	X <sup>f</sup>										8.2.4

**Table 2**  
**Schedule of Activities for Cohort 2**

Procedure	Screening		Treatment and Follow-up Period						Early Discontinuation Visit	Details in Section of CSP	
	Day -1 or Day 1	Day 1	Day 6	Day 8	Day 29	Day 85	Day 169	Day 366	Day 457	Before Day 29	After Day 29
<b>Window (days)</b>		NA	± 1	± 1	± 4	± 7	± 7	± 7	± 7		
<b>P = In-Person Visit</b> <b>H = Home Visit</b> <b>R = Remote Visit</b>	<b>P</b>	<b>P</b>	<b>P/H<sup>a</sup></b>	<b>R</b>	<b>P</b>	<b>P</b>	<b>P</b>	<b>P/R</b>	<b>P</b>	<b>P</b>	
Pregnancy testing <sup>j</sup>	X <sup>f,i</sup>	X <sup>f,i</sup>	X		X	X	X	X	X	X	8.2.4.1
Concomitant medications	X	X	X	X	X	X	X	X	X	X	6.5
Collect/update secondary contacts		X	X	X	X						8.1.2
Verify eligibility criteria	X	X									5.1, 5.2
Randomization		X									6.3.1
Survival status check			X		X	X	X	X	X	X	8.1.3
Participant-reported symptom diary <sup>k</sup>					Daily through Day 29						8.1.4
Participant-reported symptom reminder <sup>l</sup>					Daily through Day 29						8.1.4
Staff review of participant-reported symptom diary				X		X				X	
Retrieval of participant-reported symptom diary							X <sup>m</sup>			X	
Return to usual (pre-COVID-19) health				X	X	X	X	X		X	8.1.5
<b>CCI</b> ██████████										X	
Study staff-collected mid-turbinate nasal swab for SARS-CoV-2 RT-PCR and sequencing <sup>n</sup>		X <sup>f</sup>	X		X						8.1.7
<b>CCI</b> ██████████			X <sup>o</sup>	X		X	X	X			
Serum for SARS-CoV-2 serology									X	X	8.5.2.2

**Table 2**  
**Schedule of Activities for Cohort 2**

Procedure	Screening		Treatment and Follow-up Period						Early Discontinuation Visit	Details in Section of CSP	
	Day -1 or Day 1	Day 1	Day 6	Day 8	Day 29	Day 85	Day 169	Day 366	Day 457	Before Day 29	After Day 29
<b>Window (days)</b>		NA	± 1	± 1	± 4	± 7	± 7	± 7	± 7		
<b>P = In-Person Visit</b> <b>H = Home Visit</b> <b>R = Remote Visit</b>	<b>P</b>	<b>P</b>	<b>P/H<sup>a</sup></b>	<b>R</b>	<b>P</b>	<b>P</b>	<b>P</b>	<b>P/R</b>	<b>P</b>	<b>P</b>	
<b>CC1</b>											
Serum for AZD7442 pharmacokinetics	X <sup>e</sup>	X		X	X	X	X	X	X [optional]	X	X
Serum for AZD7442 anti-drug antibodies	X <sup>f</sup>			X	X	X	X	X	X [optional]	X	X
<b>CC1</b>											
<b>IMP administration</b>		X <sup>p</sup>									6
Check injection sites		X <sup>q</sup>	X <sup>r</sup>								8.2.5
Adverse events		X	X	X	X	X	X	X	X	X	8.3
SAEs and AESIs	X	X	X	X	X	X	X	X	X	X	8.3
											8.3.4

<sup>a</sup> Visits noted P/H can be performed either in-person at clinical site or at home depending on the participant's clinical status, availability of safe transfer to sites (eg, to avoid risk of infection spread), and local guidelines for travel restrictions/social distancing. For home visits, a nurse or HCP trained on study procedures will visit the participant at home; nasal swabs, blood collection (where at-home collection is possible), and inspection of injection sites will be performed by the nurse or HCP. Nurse or HCP will ensure shipment of specimens collected and reporting of AEs to study sites.

<sup>b</sup> Perform if no documentation of SARS-CoV-2 infection available; tested locally.

<sup>c</sup> Assessment will be performed only for participants attending in-person visits, or if a nurse or HCP visiting the participant at home is properly trained for these assessments.

<sup>d</sup> Height is recorded only at the screening visit.

<sup>e</sup> Perform pre-dose and 1.5 minutes ( $\pm$  5 minutes) after both injections are complete.

<sup>f</sup> Perform pre-dose on Day 1.

<sup>g</sup> Hematology panel includes coagulation markers.

- h Serum vitamin D and serum zinc, dependent on availability of laboratory kits.

i Urine pregnancy test (local laboratory) at screening. Perform another urine test (local laboratory) on Day 1 if screening urine test was performed on Day -1. Single serum (central laboratory) must be performed on Day 1. Sample urine test must return negative result before dosing.

j Urine pregnancy test (local laboratory).

k Participants will report COVID-19-related symptoms daily in an electronic device, starting pre-dose and post-dose on Day 1.

l Participant will be reminded every day through Day 29 to complete their diary. This reminder will be received through the electronic device.

m If Day 29 visit is conducted earlier in  $\pm$  4 day window, participant should retain symptom diary in order to complete required daily entries through Study Day 29.

n Mid-turbinate nasal swab is tested centrally. Sequencing applies to nasal swabs collected through Day 15.

o Pre-dose sample and post-dose sample (ie, samples obtained prior to and upon completion of IMP administered via IM injections on Day 1).

p After the sentinel group is dosed, the next 80 participants dosed (21 to 100) will undergo safety monitoring for 2 hours post IMP administration. If hypersensitivity reactions are observed in the first 100 dosed participants, subsequent participants will continue to be monitored for 2 hours post IMP administration, otherwise the minimum safety monitoring time will be 1 hour.

q Perform 30 minutes ( $\pm$  10 minutes) after the IMP has been administered and just prior to release from the study site or departure of the study staff.

r If evidence of injection site reaction persists at the Day 6 visit, the injection site will be rechecked at each visit until no evidence of an active reaction remains.

s At Day 457 AE/SAE/AESI assessment will be made by telephone only.

t Current or former smoking status to be captured.

Note: Remote (denoted by R) visit: either a phone call, or a web-based virtual assessment.

Note: Day 6 and Day 8 assessments must be performed on different days.

AESI Adverse events of special interest; COVID-19 Coronavirus disease 2019; CSP Clinical Study Protocol; ECG Electrocardiogram; HCP Healthcare personnel; IM Intramuscular; IMP Investigational medicinal product; NA Not applicable; Nab Neutralizing antibody; NP Nasopharyngeal; RNA Ribonucleic acid; RT-PCR Reverse transcription polymerase chain reaction; SAE Serious adverse event; SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2; SID Subject identification number.

## 2 INTRODUCTION

A novel coronavirus, SARS-CoV-2, first emerged in China in November 2019 causing cases of atypical pneumonia. As of 6 October 2020, the virus has spread to all corners of the globe, with over 35 million confirmed cases reported and more than one million associated deaths (Tamhane et al 2018 and WHO 2020). The COVID-19 pandemic is causing major disruption to global healthcare systems with significant socioeconomic impacts.

Effective interventions to prevent or treat COVID-19 remain few in number and clinical experience is limited.

As a response to the ongoing pandemic, AstraZeneca is developing mAbs to the SARS-CoV-2 spike protein. The SARS-CoV-2 spike 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 spike protein, antibodies can block the virus's attachment to human cells, and, therefore, is expected to block infection.

AZD7442, a combination of 2 of these mAbs (AZD8895 and AZD1061), is being evaluated for administration to treat or prevent COVID-19. There is currently one ongoing Phase I study with AZD7442 (study D8850C00001) and 2 ongoing Phase III prophylaxis studies (a pre-exposure prophylaxis of COVID-19 study D8850C00002, and a post-exposure prophylaxis of COVID-19 study D8850C00003), in addition to this treatment study.

Further details about AZD7442 are provided throughout this section and in the AZD7442 IB.

### 2.1 Study Rationale

There is an urgent need to rapidly evaluate treatments in the non-hospitalized setting, to prevent disease progression, and reduce serious complications of COVID-19 and transmission. AZD7442 is a combination of 2 mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 spike protein for neutralization of the virus. The use of 2 mAbs provides redundancy in case of virus mutation and escape. AZD8895 and AZD1061 mAbs have been engineered with triple amino acid substitutions M252Y/S254T/T256E (YTE) in the Fc region to prolong the half-life, which is expected to provide protection from COVID-19 for a duration of at least 5 months. In addition, the triple amino acid substitutions L234F/L235E/P331S I in the Fc region were engineered for both AZD8895 and AZD1061 to abrogate Fc mediated effector function, which is expected to reduce theoretical risk of antibody-dependent enhancement. The purpose of this Phase III study is to determine if AZD7442 can safely treat COVID-19 symptoms and prevent either severe COVID-19 or death.

## 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.

Summaries of nonclinical pharmacology, PK, drug metabolism, and toxicology of AZD7442 are 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.

CC1



AZD7442 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 spike 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.

### 2.3.2 Benefit Assessment

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

### 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 3 Objectives and Endpoints**

Objective	Estimand Description/Endpoint
<b>Primary</b>	
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either severe COVID-19 or death from any cause through study Day 29	<b>Population:</b> Modified full analysis set  <b>Endpoint:</b> A composite of either severe COVID-19 or death from any cause through Day 29.  Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia ( $\text{SpO}_2 < 90\%$ in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Appendix F).

**Table 3 Objectives and Endpoints**

Objective	Estimand Description/Endpoint
	<p><b>Intercurrent events:</b> The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product prior to Day 29 without already having met the primary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.</p> <p><b>Summary measure:</b> Relative risk reduction of severe COVID-19 or death from any cause in participants taking AZD7442 compared to those taking placebo during the 28-day post-dose period (Day 1 to Day 29).</p>
To evaluate safety and tolerability of a single IM dose of AZD7442 compared to placebo.	AEs, SAEs, and AESIs through end of study.
<b>Key Secondary</b>	
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either death or hospitalization <sup>a</sup> for COVID-19 complications or sequelae through Day 169	<p><b>Population:</b> Modified full analysis set</p> <p><b>Endpoint:</b> A composite of either death from any cause or hospitalization<sup>a</sup> for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169).</p> <p><b>Intercurrent events:</b> The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product or becoming unblinded to properly consider vaccination for COVID-19, prior to Day 169 without already having met the key secondary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.</p>
<b>Other Secondary</b>	
To determine if AZD7442 will prevent respiratory failure through study Day 29	The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high flow nasal cannula oxygen delivery (an oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60 liters per minute, as defined Sharma et al 2020 and Ashraf-Kashani and Kumar 2017).
To determine whether AZD7442 reduces participants' severity of participant-reported COVID-19 symptoms through Day 29	COVID-19 symptom severity assessments based on symptom severity scores over time during the 28-day period from and including the day of the dose of AZD7442 or placebo. Each symptom is scored from 0 to 4.
To determine if AZD7442 reduces the progression of participant-reported COVID-19-associated symptoms through Day 29	Progression through Day 29 of one or more COVID-19-associated symptoms to a worse status than recorded in the participant-reported symptom diary at study entry, prior to start of AZD7442 or placebo.
To determine if AZD7442 reduces SARS-CoV-2 detection or levels of RNA in nasal swabs through Day 29.	Detection (detectable versus undetectable), level, and change from baseline of SARS-CoV-2 RNA from nasal swabs through Day 29.
To evaluate differences in symptom duration between the AZD7442 and	<ul style="list-style-type: none"> <li>• Time to return to usual (pre-COVID-19) health through Day 29.</li> <li>• Duration of fever through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater</li> </ul>

**Table 3      Objectives and Endpoints**

<b>Objective</b>	<b>Estimand Description/Endpoint</b>
placebo treatment groups through Day 29	than 37.8°C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken.
To evaluate the single-dose PK of AZD7442	Serum concentration and PK parameters.
To evaluate the ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum over time.

CCI

CCI

**Table 3      Objectives and Endpoints**

Objective	Estimand Description/Endpoint
CCI	[REDACTED]

<sup>a</sup> Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic. See also Appendix H for further guidance on the definition of hospitalization.

ADA Anti-drug antibody; AE Adverse event; AESI Adverse event of special interest; AUC Area under the plasma concentration-time curve; COVID-19, Coronavirus disease 2019; ECMO Extracorporeal membrane oxygenation; CCI [REDACTED] ICU Intensive care unit; IM, intramuscular; IMP Investigational medicinal product; CCI [REDACTED] PK Pharmacokinetic; RNA Ribonucleic acid; SAE Serious adverse event; SARS-CoV-2 Severe acute respiratory syndrome-coronavirus-2; SpO<sub>2</sub> Oxygen saturation; WHO World Health Organization.

Additional exploratory objectives will be considered.

## **4            STUDY DESIGN**

### **4.1        Overall Design**

This is a Phase III, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of a single 600 mg IM dose of AZD7442 compared to placebo for the treatment of COVID-19. Participants will also receive the standard of care treatment for COVID-19 in the participating clinic. Approximately 130 to 140 sites will participate in this study.

Participants will be outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1.

At least 60% of participants will meet the protocol definition of being at high-risk of progression to severe COVID-19 as defined by any of the following:

- Persons aged 65 years and older at randomization

- Persons aged < 65 years and having at least one of the following conditions:
  - Cancer
  - Chronic lung disease or moderate to severe asthma
  - Overweight (defined as a body mass index (BMI) > 25 kg/m<sup>2</sup> but < 30 kg/m<sup>2</sup>) or obesity (BMI ≥ 30 kg/m<sup>2</sup>); may be based on self-report of recent height and weight measurement)
  - Hypertension
  - Cardiovascular disease (including history of stroke)
  - Diabetes
  - Chronic kidney disease
  - 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
  - Sickle cell disease
  - Smoking (current or former)

Randomization will be stratified (using centralized blocked randomization) by:

- 1 Time from symptom onset ( $\leq$  5 days versus > 5 days)
- 2 High-risk versus low-risk of progression to severe COVID-19 (high-risk is defined above)

The enrollment of low-risk participants has stopped.

Up to approximately 1700 participants will be randomized in a 1:1 ratio to receive a single IM dose of 600 mg of AZD7442 (n = up to approximately 850) or placebo (n = up to approximately 850) on Day 1. The first 20 participants to be dosed at selected sites will form a sentinel group. To ensure balanced size of the two treatment groups in the sentinel group, randomization of these sentinel participants will be in a 1:1 ratio without stratification. After the entire sentinel group has been dosed, further enrollment will pause until the sentinel group's safety data through Day 8 has been reviewed by the DSMB in order to provide a recommendation to continue or to halt dosing of additional participants.

Participants will be enrolled into one of 2 independent cohorts:

- Cohort 1 (n = approximately 300), which will include the sentinel group, will undergo more intensive testing to characterize their virological and immunological status, and to correlate that status with clinical outcomes.

- Cohort 2 (n = up to approximatley 1400) will be followed for clinical outcomes.

Following screening, and no more than 7 days from self-reported onset of COVID-19-related symptoms or measured fever, participants will be randomized on Day 1 and receive a single dose of IMP. The dose will be administered as 2 separate IM injections (one for AZD8895 and one for AZD1061; the 2 compounds will not be co-administered) in the gluteal region. In Cohort 1, the first 20 participants dosed (ie, the sentinel group) will undergo safety monitoring for 4 hours post IMP administration before further participants are dosed. At each site, there will be an interval of 24 hours after dosing of the first participant in the sentinel group before the next participant can be dosed. The next 80 participants (21 to 100) will then undergo safety monitoring for 2 hours post IMP administration. If hypersensitivity reactions are observed in the first 100 participants, subsequent participants will continue to be monitored for 2 hours post IMP administration, otherwise the minimum safety monitoring time will be 1 hour. In addition, the sentinel group will be contacted daily (in-person or by telephone) for the first 4 days after IMP administration. The study will be temporarily suspended if the criteria listed in Section 7.4 are met. All sites will have access to emergency kits for treatment of severe anaphylactic reactions/shock and to medical staff trained in using these emergency kits.

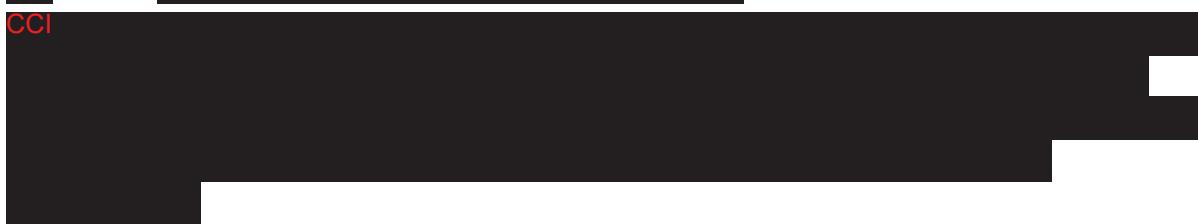
After administration of the dose of study intervention on Day 1, participants will undergo 28 days of intensive follow-up, followed by limited follow-up through visit Day 457.

An independent DSMB will monitor safety throughout, including the safety data through Day 8 from the participants in the sentinel group. The primary analysis for efficacy will be conducted by the Sponsor or its delegates 30 days after approximately 43 primary endpoint events have been confirmed in the primary analysis population. Enrollment will stop when approximately 43 primary events have been confirmed in the primary analysis population. A Day 169 analysis (additional efficacy and safety) will be conducted when all participants have been followed through Day 169. A final analysis will be conducted when all participants have completed the study. See Section 9.6 for further details.

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#### **4.4 End of Study Definition**

A participant is considered to have completed the study if he/she has completed all stages of the study, including the last scheduled procedure shown in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA 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  $\geq$  18 years of age inclusive at the time of signing the informed consent.

##### **Type of Participant and Disease Characteristics**

- 2 Participant who has a documented laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (eg, oropharyngeal, NP, or nasal swab, or saliva) collected  $\leq$  3 days prior to Day 1.
- 3 WHO Clinical Progression Scale score  $> 1$  and  $< 4$ .
- 4 Participant must be dosed with IMP no more than 7 days from self-reported onset of COVID-19-related symptoms (mild to moderate COVID) or measured fever, defined as the self-reported date of first reported sign/symptom from the following list:
  - Subjective fever or feeling feverish
  - Cough
  - Shortness of breath or difficulty breathing at rest or with activity
  - Sore throat
  - Body pain or muscle pain/aches
  - Fatigue
  - Headache
  - Chills
  - Nasal obstruction or congestion

- Nasal discharge
  - New loss of taste or smell
  - Nausea or vomiting
  - Diarrhea
  - Documented temperature > 37.8°C/100°F
  - New onset confusion (only for participants ≥ 60 years old)
  - Appetite loss or decreased food intake (only for participants ≥ 60 years old)
  - Increased supplemental oxygen requirement (only for participants on baseline supplemental oxygen)
- 5 One or more of the following signs/symptoms must be present within 24 hours prior to Day 1:
- Cough
  - Sore throat
  - Shortness of breath or difficulty breathing at rest or with activity
  - Body pain or muscle pain/aches
  - Fatigue
  - Headache
  - Chills
  - Nasal obstruction or congestion
  - Nasal discharge
  - Nausea or vomiting
  - Diarrhea
  - New loss of taste or smell
- 6 Oxygenation saturation of ≥ 92% obtained at rest by study staff within 24 hours prior to Day 1, unless the potential participant regularly receives chronic supplementary oxygen for an underlying lung condition.

#### **Participation in another COVID-19 treatment trial**

- 7 Agrees not to participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period until reaching hospitalization or 28 days post-entry, whichever is earliest.

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- 8 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 90 days following administration of 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 amenorrheic 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 amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
    - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.
  - Women 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 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 pregnancy test result at Visit 1 and during the study as in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2).

Examples of highly effective birth control methods are listed below.

- Intrauterine device
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

- Vasectomized partner (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).
- Sexual abstinence (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).
- Combined (estrogen- and progestogen-containing hormonal contraception)
  - Oral (combined pill)
  - Injectable
  - Transdermal (patch)
- Progestogen-only hormonal contraception
  - Oral
  - Injectable
  - Implantable

### **Informed Consent**

- 9 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative) based on the assessment of the investigator.
- 10 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 History or current hospitalization for COVID-19 [see also Appendix H for further guidance on the definition of hospitalization].
- 2 Current need for hospitalization or immediate medical attention in a clinic or emergency room service in the clinical opinion of the site investigator [see also Appendix H for further guidance on the definition of hospitalization].
- 3 Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.

- 4 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 administration immediately after enrollment
- 5 Current requirement for mechanical ventilation or anticipated impending need for mechanical ventilation.
- 6 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- 7 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.
- 8 Known allergy/sensitivity or any hypersensitivity to components of the IMP or placebo.
- 9 Any co-morbidity requiring surgery within 7 days prior to study entry, or that is considered life-threatening in the opinion of the site investigator within 30 days prior to study entry.

#### **Prior/Concomitant Therapy**

- 10 Use of any prohibited medication listed in Section 6.5 within 30 days or 5 half-lives, whichever is longer, prior to study entry.
- 11 Receipt of convalescent COVID-19 plasma treatment at any time prior to study entry.
- 12 Receipt of systemic steroids (eg, prednisone, dexamethasone) or inhaled steroids within 30 days prior to study entry unless a stable dose used for a chronic condition.

#### **Prior/Concurrent Clinical Study Experience**

- 13 Receipt of any IMP in the preceding 90 days or 5 half-lives, whichever is longer, or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

#### **Other Exclusions**

- 14 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
- 15 Previous randomization in the present study.
- 16 For women only, currently pregnant (confirmed with positive pregnancy test) or breast feeding.
- 17 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomization.
- 18 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.

- 19 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**

- 1 Participants must follow the contraception requirements outlined in Section 5.1.
- 2 Restrictions relating to concomitant medications are described in Section 6.5.

### **5.4 Screen Failures**

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to 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 re-screened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility. Only a single re-screening is allowed in the study. Re-screened participants should be assigned the same participant number as for the initial screening. Individuals who are re-screened do not need to re-consent 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.

### **6.1 Investigational Medicinal Products Administered**

#### **6.1.1 Investigational Medicinal Products**

Participants will be randomized in a 1:1 ratio to receive one single 600 mg dose of AZD7442 (administered as a 3 mL IM injection containing 300 mg AZD8895 and a 3 mL IM injection containing 300 mg AZD1061) or saline placebo (administered as 2 separate 3 mL IM injections) (Table 4). Investigational medicinal product will be administered on Day 1, and participants will be monitored for 456 days after IMP administration.

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IMP Investigational medicinal product; IM Intramuscular; w/v Weight/volume.

## 6.2 Preparation/Handling/Storage/Accountability

- 1 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.
- 2 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.
- 3 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).

### **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.

AZD7442 (AZD8895 and AZD1061) or placebo should be administered intramuscularly with one 3.0 mL injection in each gluteal region. The 2 drug products, 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. Refer to Handling Instructions for detailed dose preparation and administration information.

## **6.3        Measures to Minimize Bias: Randomization and Blinding**

### **6.3.1      Randomization**

All participants will be centrally assigned to 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 (using centralized blocked randomization) by:

- 1 Time from symptom onset ( $\leq$  5 days versus  $>$  5 days)
- 2 High-risk versus low-risk of progression to severe COVID-19 (high-risk is defined in Section 4.1)

The enrollment of low-risk participants is stopped.

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 study intervention received. Since 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 randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization, or in the instance a participant wishes to be considered for a SARS-CoV-2 vaccine. The investigator documents and reports the action to 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' IMP assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's IMP assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind.

## **6.4 Investigational Medicinal Product Compliance**

Dosing will take place under the guidance of study personnel. The date (and time, if applicable) of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. If a problem occurs during dosing, such as needle break, no re-dosing is permitted.

## **6.5 Concomitant Therapy**

Permitted, prohibited, and restricted medications are summarized in Table 5.

Any medication or vaccine (including 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 5      Summary of Permitted, Prohibited, or Restricted Medications**

Use Category	Type of Medication/treatment	Timeline/instructions
Permitted	Routine vaccines <sup>a</sup>	Licensed influenza vaccines are permitted at any time. All other routine vaccines are permitted beginning > 30 days after IMP dose
	Allergen immunotherapy	Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Day 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 treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted.
	Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, hydroxychloroquine, or cytotoxic chemotherapy)	Allowed, provided the participant is stable on maintenance dose (at steady state) prior to Day 1 and up to Day 29, OR Allowed if participant is hospitalized for treatment of COVID-19
	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.	
Prohibited	<ul style="list-style-type: none"> <li>• Investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19</li> <li>• Hydroxychloroquine</li> <li>• Chloroquine</li> <li>• Ivermectin</li> <li>• HIV protease inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>• Note: For participants who become hospitalized with COVID-19, receipt of approved/licensed treatment options are permitted and they should be treated according to local standard of care, including investigational agents under emergency use authorization or equivalent regulations.</li> <li>• Use of hydroxychloroquine is acceptable if used chronically for autoimmune disease, and the dose is stable prior to Day 1 and up to Day 29.</li> <li>• Use of chloroquine if used to treat a parasitic infection</li> <li>• Use of ivermectin is acceptable if used to treat a parasitic infection</li> <li>• HIV protease inhibitors are acceptable if used chronically for HIV infection, and the dose is stable prior to Day 1 and up to Day 29.</li> </ul>

**Table 5 Summary of Permitted, Prohibited, or Restricted Medications**

Use Category	Type of Medication/treatment	Timeline/instructions
	<ul style="list-style-type: none"><li>COVID-19 vaccine<sup>a</sup></li></ul>	<ul style="list-style-type: none"><li>It is expected that most participants in this trial would have a protective infection-induced immune response. At this time, we have no reason to believe that the protection afforded by natural infection is less frequent or less robust than the protection provided by any vaccine and hence may not be required during acute illness.</li><li>If participants request vaccination, the procedures described below apply.</li></ul>
Restricted	Contraceptive methods	See Section 5.1
	Blood/plasma donation	Participants must abstain from donating blood or plasma from the time of informed consent for one year after dose of study drug.
	Ova/Sperm donation	See Sections 8.3.10.1 and 8.3.10.2

<sup>a</sup> The potential impact of AZD7442 on COVID-19 vaccines is not known and has not been studied. See Section 6.5.1 for instructions on COVID vaccinations.

COVID-19 Coronavirus disease 2019; HIV Human immunodeficiency virus; IMP Investigational medicinal product; SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2.

### **6.5.1 COVID-19 Vaccination**

Participants who have received COVID-19 vaccination prior to study entry will be excluded from this study.

During the study, when participants become eligible for access to a SARS-CoV-2 vaccine, it is appropriate that they can discuss with the investigator and others after Day 30 so as to make an informed choice. The following considerations apply:

- Participants should not receive vaccination with an anti-SARS-CoV-2 vaccine during their acute illness.
  - Participants in this study will have active COVID-19 at the time of enrollment. Administration of vaccines during acute infectious illness is generally discouraged as a matter of standard clinical practice. Even with an effective vaccine, potentially protective immunological responses should take approximately 2 weeks to begin to appear. No clinical data, nor good immunological rationale, exist to suggest that vaccination with an anti-SARS-CoV-2 vaccine will have a beneficial effect on acute COVID-19.
- Participants in this study are unlikely to receive any benefit from vaccination with an anti-SARS-CoV-2 vaccine after recovery from COVID-19.
  - There is no evidence that shows that participants will benefit from vaccination with an anti-SARS-CoV-2 vaccine after recovery from their acute COVID-19.

- After recovery from COVID-19, most participants in this trial would have a protective infection-induced immune response. 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 any vaccine.
- Participants may wish to be vaccinated. If so, they may be unblinded as to their randomized investigational treatment in this study as per study unblinding procedure (Section 6.3.3), counselled, and referred outside the study for possible vaccination.
  - Despite the lack of evidence or a rationale that participants in this study are likely to benefit from receiving a SARS-CoV-2 vaccine, some may wish to be vaccinated. In such situations, after recovery from their COVID-19, and appropriate counselling, such participants can be unblinded as to their randomized investigational treatment in this study. With that information, they can be further counselled:
    - 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, in the presence of adequate neutralizing antibody titers, an appropriate and effective response to the vaccine might be impaired. Such participants should be advised to consider waiting an appropriate length of time (9 to 12 months) before receiving an anti-SARS-CoV-2 vaccine. For AZD7442, 9 to 12 months will represent 3 or 4 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.
    - After such counselling, the decision to receive the vaccine should be left to the participants and his or her personal physician.

Participants who have been unblinded in order to receive vaccination can and should remain in the study after being unblinded.

## **6.6 Dose Modification**

The IMP will be administered as described in Section 6.1.1. Dose modification is not permitted unless in case of discontinuation of IMP, as per investigator's clinical judgment. Re-administration of dose (re-challenge) 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 Investigational Medicinal Product**

Participants will receive a single dose of 600 mg AZD7442 (administered as a single IM injection containing 300 mg AZD8895 and a single IM injection containing 300 mg AZD1061) or saline placebo.

It may be necessary for a participant to temporarily interrupt their injection of IMP. If the injection of IMP is not resumed (ie, it is discontinued), the participant should remain in the study to be evaluated.

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

### **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 (Table 1 for Cohort 1 and Table 2 for Cohort 2). See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- 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 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 survival status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get the IMP. Public sources may be searched for survival status information. If survival 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 survival 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 participants experience a grade 4 hypersensitivity reaction or hypersensitivity reaction classified as an SAE.
- If 2 or more participants, within the first 100 participants, experience a grade 3 or higher hypersensitivity reaction.
- If 2 or more participants, within the first 100 participants, experience a grade 3 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).

## **8 STUDY ASSESSMENTS AND PROCEDURES**

- Study procedures and their timing are summarized in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2). 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 have met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

### **8.1 Efficacy Assessments**

#### **8.1.1 Clinical Assessments**

Supplemental oxygen use will be recorded at each in-person visit.

At study entry, if peripheral oxygen saturation is < 92% on usual supplemental oxygen requirements, the participant should be referred for emergency department evaluation and should not initiate IMP.

During follow-up in-person visits (after Day 1) through Day 29, peripheral oxygenation saturation measures < 96% should be reviewed by an investigator and referral for medical attention made at the discretion of the investigator.

The participant should be assessed for severe COVID-19, characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia ( $\text{SpO}_2 < 90\%$  in room air and/or severe respiratory distress) and a score of 5 or higher in the WHO Clinical Progression Scale in Appendix F.

### **8.1.2      Collect/Update Secondary Contacts**

Sites will capture contact information for at least 2 individuals that the site can contact if the participant cannot be reached (eg, spouse, friend, neighbor). Sites will also request healthcare provider contact information and hospital(s) that the participant is likely to go to if they get sick.

Contact information for secondary contacts or healthcare provider will not be recorded on any eCRF.

On Day 1 only, sites will record the participant's home address in site records (it will not be reported on an eCRF).

### **8.1.3      Survival Status Check**

If a participant cannot be reached after 2 attempts 24 hours apart, then their listed secondary contact person(s) or healthcare provider will be contacted for a check of the participant's survival status.

### **8.1.4      Participant-reported Symptom Diary**

During the first 28 days, participants will be asked to report their COVID-19 symptoms and temperature in provisioned devices provided to each participant to enable assessments every 24 hours at home.

On Day 1, participants will be trained by the site staff on how to complete the diary. It is important that the participant responds to questions without being influenced by anyone else. Day 1 assessments must be completed before administering IMP. Participants will be asked to complete subsequent entries in the diary each evening on Day 1 through 29 (the entry on Day 29 may be completed with the site staff during the Day 29 visit, if the visit occurs on Day 29 versus another day in the Day 29 visit window).

The diary will ask participants to report on the following:

- Temperature
- Shortness of breath
- Difficulty breathing
- Chills
- Cough
- Fatigue
- Muscle aches
- Body aches

- Headache
- Loss of taste
- Loss of smell
- Sore throat
- Congestion
- Runny nose
- Nausea
- Vomiting
- Diarrhea

Symptom severity scoring will be based on the participant's self-assessment. Participants should use the same self-determined approach to severity scoring each day.

Only participants  $\geq$  60 years of age will be asked to report on the following:

- Have you felt as if you can't think clearly?
- Have you experienced any loss or decrease in appetite?
- Do you take supplemental oxygen?
- If yes, have you needed to increase your supplemental oxygen intake?

The participant-reported symptom diary is in Appendix G.

In the event an electronic device is not available when the participant is randomized, there will be a paper diary alternative with detailed instructions for participants and site staff.

### **Diary Reminder and Staff Review of Diary**

Participant will be reminded every day through Day 29 to complete their diary. This reminder will be received through the electronic device.

The diary will be reviewed by study staff in person with each participant according to the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2). If an appropriate electronic system is available, the participant's diary entries will automatically be captured in the eCRF. If such a system is not available, the participant's answers on the diary will be transcribed into the eCRF.

Participants who report worsening symptoms from any cause during the study may be referred to their healthcare provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, ie, hospitalization or death.

Situations in which a COVID-19 sign or symptom should be reported as an AE are described in Section 8.3.8.

### **8.1.5      Return to Usual Health**

If the participant returns to usual (pre-COVID-19) health at any time through Day 169, the date will be recorded per the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2).

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At subsequent visits per the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2), participants will be asked if any new household members have been diagnosed with SARS-CoV-2 infection, and the response recorded on the eCRF.

### **8.1.7      Virologic Studies**

Mid-turbinate nasal swabs and plasma will be collected for qualitative and quantitative SARS-CoV-2 RNA assessment.

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#### **Mid-turbinate Nasal Swabs**

Mid-turbinate nasal swabs will be taken at in-person visits per the SoA and will be analyzed centrally by an authorized or approved RT-PCR assay (Table 1 for Cohort 1 and Table 2 for Cohort 2). The Day 1 swab should be collected prior to the dose of IMP.

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## **8.2          Safety Assessments**

Planned time points for all safety assessments are provided in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2).

### **8.2.1       Physical Examinations**

A complete physical examination will be performed at screening, followed by a targeted or complete physical examination at subsequent visits per the SoA in Table 1 for Cohort 1 and

Table 2 for Cohort 2.

- A complete physical examination will include, but not be limited to, assessment of height (screening only), 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. When there are no new complaints or findings this should be documented. Each clinically significant abnormal finding following randomization should be reported per Section 8.3 (AE/SAE reporting).

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 pulse rate, pulse oximetry, blood pressure, and body temperature will be performed at time points specified in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2). The participant should be resting prior to the collection of vital signs.

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

### **8.2.3 Electrocardiograms**

A triplicate 12-lead ECG will be performed at time points specified in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2). 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 (Table 1 for Cohort 1 and Table 2 for

Cohort 2).

Additional safety samples may be collected, if clinically indicated, at the discretion of the investigator. The date and 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. Instructions for the collection and handling of the samples will be provided in the study-specific Laboratory Manual. If, due to COVID-19 restrictions, samples cannot be sent to the central laboratory the safety laboratory assessments may be performed at a local laboratory possessing current standard certification for its jurisdiction.

The following laboratory variables will be measured.

<b>Hematology</b>	
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
<b>Serum Clinical Chemistry</b>	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total Bilirubin
Calcium	Conjugated bilirubin
Phosphate	Creatine kinase
Glucose	
C-reactive protein (CRP)	
<b>Urinalysis</b>	
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)	

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

TBL Total bilirubin; ULN Upper limit of normal.

#### 8.2.4.1 Females Only

Pregnancy test (women of childbearing potential only)	
Serum human beta chorionic gonadotrophin (screening, at central laboratory)	Urine human beta chorionic gonadotrophin (locally)
Pregnancy test (suspected postmenopausal women < 50 years only)	
Follicle-stimulating hormone (FSH) (using serum at screening, at central laboratory)	

#### 8.2.5 Injection Site Inspection

An inspection of the injection sites should be performed on Day 1 (as according to Table 6), and at subsequent in-person visits up to and including Day 6 (see SoA in Table 1 for Cohort 1 and Table 2 for Cohort 2). If evidence of injection site reaction persists at Day 6 visit, the injection site will be rechecked at each visit until no evidence of an active reaction remains.

**Table 6** Injection Site Inspection on Day 1

Procedure/Time after both injections have been administered	Immediately after IMP administration	30 minutes ( $\pm 10$ 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.

In Cohort 1, the first 20 participants dosed (ie, the sentinel group) will undergo safety

monitoring for 4 hours post IMP administration before dosing further participants. At each site, there will be an interval of 24 hours after dosing of the first participant in the sentinel group before the next participant can be dosed. The next 80 participants (21 to 100) will undergo safety monitoring for 2 hours post IMP administration and, if no hypersensitivity reactions are observed, the remaining participants will undergo safety monitoring for at least 1 hour post IMP administration. Should hypersensitivity reactions be observed in the first 100 participants, all participants will be monitored for safety monitoring for 2 hours post IMP administration.

For the first 4 days after IMP administration, the sentinel group will be contacted daily (in-person or by telephone) 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).

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**

Non-serious AEs 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 the ICF throughout the study, up to and including the last visit.

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
- 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 study (yes or no)
- Outcome

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

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

The following severity ratings will be used:

- Grade 1: An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. 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. 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. 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.
- Grade 5: Death as result of an event.

It is important to distinguish between serious and severe AEs:

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

### **8.3.3 Causality Collection**

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

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

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

### **8.3.4 Adverse Events of Special Interest**

AESIs will be collected according to the time points specified in the SoA (see Table 1 for Cohort 1 and Table 2 for Cohort 2).

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
- Injection site reactions

### **8.3.5 Adverse Events Based on Signs and Symptoms**

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

See Section 8.3.8 for the reporting of COVID-19-related symptoms.

### **8.3.6 Adverse Events Based on Examinations and Tests**

The results from the protocol-mandated laboratory tests 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 fulfil 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 is not limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or drug interruption).

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

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

### **8.3.7 Hy's Law**

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT  $\geq 3 \times$  ULN together with TBL  $\geq 2 \times$  ULN and confirmed as a HL case should be reported as a 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, or another drug) should be evaluated. The elevation in

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

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

### **8.3.8 Disease Under Study**

AZD7442 treatment studies will take a consistent approach to the handling of symptoms related to COVID-19, the disease under study.

COVID-19 symptoms or signs, such as fever, cough, shortness of breath/difficulty breathing, sore throat, body/muscle pain, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, new loss of taste or smell, nausea, vomiting, diarrhea, new onset confusion (only for participants  $\geq$  60 years old), appetite loss or decrease food intake (only for participants  $\geq$  60 years old), increased supplemental oxygen requirement (only for participants on baseline supplemental oxygen) will be recorded as AEs when any of the following occur:

- The sign or symptom is serious according to the definition in Appendix B 2.
- The participant discontinues the study due to the sign or symptom.
- In the investigator's judgment, the sign or symptom is not considered COVID-19 related.

### **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. The SAE must also be entered into the EDC system when it is available again.

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.

## Ova Donation

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

### 8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child during the study and for 365 days following the administration of IMP.

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.

## Sperm Donation

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

### 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 **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

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

## 8.4 Overdose

For this study, any dose of AZD7442 > 600 mg (ie, AZD8895 > 300 mg or AZD1061 > 300 mg) will be considered an overdose.

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

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

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

## 8.5 Human Biological Samples

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

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

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

### 8.5.1 Pharmacokinetics Assessments

- Serum samples will be collected for measurement of serum concentrations of AZD7442 (AZD8895 and AZD1061), as specified in the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2).

- 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 analyze 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.

#### **8.5.1.1 Determination of Drug Concentration**

Samples for determination of drug concentration in serum will be assayed 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.

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#### **8.5.2.1 Anti-drug Antibody**

Blood samples for determination of ADA in serum will be assayed using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report. Samples will be collected, labeled, stored, and shipped, as detailed in the Laboratory Manual.

#### **8.5.2.2 SARS-CoV-2 Serology**

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the SoA (Table 1 for Cohort 1 and Table 2 for Cohort 2). Baseline

serostatus and time to seroconversion in participants receiving AZD7442 versus placebo may be determined in a validated SARS-CoV-2 nucleocapsid antigen assay operated by an authorized laboratory. Serologic assessment to S (spike), RBD, and nucleocapsid antigens may also be assessed quantitatively using a validated multiplexed MSD immunoassay.



## **8.6 Human Biological Sample Biomarkers**

### **8.6.1 Collection of Mandatory Samples for Biomarker Analysis**

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

Samples for biomarker research are required and will be collected from participants, as specified in the SoA (see Table 1 for Cohort 1 and Table 2 for Cohort 2). **CCI** [REDACTED]

[REDACTED] Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

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## **8.7 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 classified as either having severe COVID-19 symptoms or death from any cause, or not. Efficacy will be calculated as the RRR, defined as 1–Relative Risk. The null hypothesis is the RRR of severe COVID-19 or death from any cause through Day 29 in participants on AZD7442 compared with those on placebo is equal to zero. The alternative hypothesis is that the RRR is not equal to zero.

The primary efficacy endpoint will be formally assessed at one primary analysis 30 days after

approximately 43 primary endpoint events have been confirmed in the primary analysis population. The type I error rate will be controlled by a 2-sided alpha = 0.05. The methodology used to conserve alpha is detailed in Section 9.4.5.

## 9.2 Sample Size Determination

Enrollment of up to approximately 1700 participants is planned. At least 60% of participants will meet the protocol definition of being at high-risk of progression to severe COVID-19 (see Section 4.1 for definition of high-risk).

**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, can be re-screened once. If they are not subsequently randomly assigned in the study, they are considered “screen failures”.

Up to approximately 1700 participants, allowing for variability of the placebo groups primary endpoint event rate, will be randomized in a 1:1 ratio to receive a single IM 600 mg dose of AZD7442 (n = up to approximately 850) or placebo (n = up to approximately 850) on Day 1.

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This is an event-driven study with a primary analysis initiated 30 days after approximately 43 primary endpoint events have occurred in the primary analysis population. The study CCI [REDACTED] to detect a relative reduction CCI [REDACTED] in the incidence of severe COVID-19/death between the study groups (AZD7442 vs placebo), CCI [REDACTED]



## 9.3 Populations for Analyses

The following populations are defined in Table 7.

**Table 7      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.

**Table 7      Populations for Analysis**

Population/Analysis Set	Description
Full analysis set	All randomized participants who received 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 or assent to participate in the study will be included up to the date of their study termination.
Modified full analysis set	All participants in the full analysis set who received IMP $\leq$ 7 days from symptom onset and were not hospitalized at baseline ( $\leq$ Day 1) for isolation purposes.
Early intervention analysis set	All participants in the modified full analysis set who received IMP $\leq$ 5 days from symptom onset.
Seronegative analysis set	All participants in the modified full analysis set who were seronegative at baseline.
Safety analysis set	The safety analysis set consists of all participants who have received 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 received active IMP is classified as active.
PK analysis set	Dosed participants for whom an adequate (measurable drug concentration) PK profile has been obtained. 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.
Virology analysis set	The Virology analysis set consists of all participants in Cohort 1, who undergo more intensive virologic and immunologic assessments. Participants will be analyzed according to their received treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.

IMP Investigational medicinal product; PK Pharmacokinetic.

## 9.4      Statistical Analyses

The first version of the SAP was finalized prior to the first meeting of the DSMB and it includes 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 be completely double-blind until the primary analysis (ie, blind for participants, Investigators/site staff, and Sponsor/designated clinical research organization), in which case members of Sponsor/designated clinical research organization associated with the analysis,

write-up and submission will be unblinded. The site personnel, participants, and the study team members who participate in the advice or decisions involving study conduct or day-to-day interactions with the site, will remain blinded until the end of the study (ie, all participants have completed Day 457 visit) to ensure the trial integrity is maintained.

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.

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## 9.4.2 Efficacy

### 9.4.2.1 Primary Endpoint(s)

The primary efficacy endpoint is a composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia ( $\text{SpO}_2 < 90\%$  in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Appendix F).

The primary estimand will be used for the analysis of the primary efficacy endpoint. It will be based on participants in the modified full analysis set defined in Table 7. CCI



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For the primary efficacy analysis, the stratified CMH method will be used. The RR will be estimated by the CMH method, and the efficacy will be calculated as the  $RRR = 100 \times (1-RR)$ , which represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to the placebo group. The 95% 2-sided CI will be presented. Participants who do not have an event and do not remain in the study until the Day 29 assessment, will be treated as having a missing primary endpoint.

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To support the primary analysis, Kaplan-Meier curves for time to severe COVID-19 or death from any cause during the first 28 days of follow-up will be generated for each randomized group. The Kaplan-Meier cumulative incidences will be reported. A stratified Log-Rank test will be conducted to assess the difference between the curves. A Cox-Proportional Hazards model will be conducted to obtain hazard ratios and their respective 95% CIs. The stratification factors will be included as covariates in the Cox model. Absence of data following participants' withdrawal/lost to follow-up will be treated as missing and censored at the date of last known status. Additionally, the absolute risk reduction of AZD7442 with respect to placebo in preventing severe COVID-19 or death from any cause at Day 29, will be presented, along with the 2-sided 95% CI using the stratified Miettinen and Nurminen's score method (Miettinen and Nurminen 1985).

#### 9.4.2.2 Secondary Endpoint(s)

The key secondary endpoint is a composite of either death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169) and will be analyzed in participants in the modified full analysis set.

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For the key secondary efficacy analysis, the RRR will be calculated at Day 169, as described for the primary efficacy analysis. The analysis will be conducted once, when all participants complete their Day 169 visit. The point estimate of the RRR of the key secondary endpoint by AZD7442 compared to placebo, as well as the 95% CI, will be calculated and reported following the same methodology as described for the primary efficacy analysis. The null hypothesis that “the RRR of the key secondary efficacy endpoint by AZD7442 compared to placebo is equal to zero” will be tested at an alpha level of 5%. The key secondary efficacy endpoint will only be considered statistically significant if the statistical significance of the primary efficacy endpoint and all supportive estimands for the primary endpoint is demonstrated. If the significance of the primary efficacy endpoint and all supportive estimands is not achieved, then the p-value for testing the key secondary efficacy endpoint will be considered nominal.

To support the key secondary analysis, Kaplan-Meier curves for time to death from any cause or first hospitalization for COVID-19 complications or sequelae during the Day 169 follow-up will be generated for the 2 treatment groups. The Kaplan-Meier cumulative incidences will be reported. A stratified Log-Rank test will be conducted to assess the difference between the curves. A Cox-Proportional Hazards model will be used to obtain hazard ratios and their respective 95% CIs. The stratification factors will be included as covariates in the Cox model.

Other secondary endpoints, that are derived from binary outcomes or have binary outcome components, will be analyzed and reported similarly using the primary analysis statistical method, except for detectability, and include:

- The proportion of participants with respiratory failure, through Day 29, defined as a requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high flow cannula oxygen delivery.

- The proportion of participants with progression, through Day 29, of one or more COVID-19-associated symptoms to worse status than recorded in the participant-reported symptom diary entry prior to start of AZD7442 or placebo.

The proportion of participants with undetectable SARS-CoV-2 over time (through Day 29) will be analyzed using a Kaplan-Meier analysis for time to first undetectable result. This analysis will only be conducted in the Virology analysis set.

The proportion of participants who return to usual health over time (through Day 29) will also be analyzed using a Kaplan-Meier analysis for time to return to usual health.

The only difference in the analysis and reporting of these secondary endpoints, compared to the key secondary endpoint, is that all CIs and p-values will be considered nominal.

For non-binary components and endpoints, the following methods of analysis are planned.

- The change from baseline of SARS-CoV-2 RNA, and RNA levels at each treatment visit, from nasal swabs will be summarized using descriptive statistics. For Cohort 1, treatment groups will be compared at each post-baseline assessment using a Mixed Model for Repeated Measures. This analysis will be conducted at the interim analysis. For all participants pooled, ie, Cohort 1 and Cohort 2, treatment groups will be compared at Day 6 using an Analysis of Covariance model. Both models will include baseline values as a fixed covariate.
- Duration of fever, and time to return to usual health through Day 29, will be summarized using descriptive statistics. Treatment groups will be compared using a 2-sided Wilcoxon Rank Sum test at an alpha level of 5%. The Hodges-Lehmann estimate and its 95% CI for the location shift between the 2 groups will be reported.
- Participant-reported COVID-19 symptom severity assessments will be summarized by symptom and over time using descriptive statistics to tabulate actual and change from baseline summaries. A mixed model for repeated measures may be used to assess differences between treatment groups over time. For each symptom, shift tables will be used to show the proportion of participants shifting from baseline severity score to maximum post-baseline severity score. For each symptom, the proportion of participants who experienced a  $\geq$  1-point reduction in severity from baseline to maximum severity post baseline will be tabulated.

Details regarding the calculation of these endpoints and related imputation (if applicable), will be described in the SAP.

Specific technical details will be documented and explained in the SAP.

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### 9.4.3 Safety

#### 9.4.3.1 Primary Endpoint(s)

The safety of AZD7442 will primarily be assessed by:

- Incidence of AEs through end of study
- Incidence of SAEs through end of study
- Incidence of AESIs through end of study

AE intensity will be graded according to Appendix B 2. 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)
- Vital signs (pulse rate, pulse oximetry, blood pressure, and body temperature)
- Physical examination
- ECG

Laboratory assessments will be performed for hematology, clinical chemistry, coagulation, and urinalysis parameters.

All parameters from laboratory, vital signs, physical examination, and ECG 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.

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#### 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, race, ethnicity, region, time from symptom onset to IMP, risk groups defined as 'high' or 'low', comorbidity, baseline levels of vitamin D and zinc, standard of care, and baseline serostatus. Given data availability,

efficacy by viral variants may be explored. 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 Analysis**

Not applicable.

## **9.6        Data Safety Monitoring Board**

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study. They will review safety data through Day 8 from the sentinel group in Cohort 1 composed of the first 20 participants to be dosed (approximately 10 participants allocated to the AZD7442 group and 10 allocated to the placebo group) and provide a recommendation to continue or to halt dosing of additional participants.

The DSMB will make any necessary recommendations to the Sponsor based on their evaluations of emerging safety data. For details on the DSMB, refer to Appendix A 5. In addition, the composition and operation of the independent DSMB will be described in a DSMB Charter.

## **10        SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

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

### A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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 IB 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 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 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.

A participant who is re-screened is not required to sign another ICF.

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

## **A 4 Data Protection**

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable, will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## **A 5 Committee 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 independent DSMB will monitor and protect the safety of the participants throughout 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.

The DSMB will review safety data on a regular basis as set out in the DSMB Charter, including, but not limited to, reviewing the safety data through Day 8 from all participants in the sentinel group.

The DSMB can recommend modifications of the protocol to enhance participant safety and to recommend 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 on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality, such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in 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 verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## **A 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 study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any 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 multicenter 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 (for example 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 fulfils one or more of the following criteria:

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

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

### **Life-threatening**

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

### **Hospitalization**

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

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

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

### **Severity Rating Scale:**

- Grade 1: An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. 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. 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. 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.
- 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 no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as ‘not related’.

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

## B 4 Medication Error

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

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

Medication error includes situations where an error:

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

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

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

- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

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

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 during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is 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 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, for example, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

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

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

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

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

### **D 1 Introduction**

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

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

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

The investigator will also review AE data (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 Drug Induced Liver Injury (DILI) caused by the IMP.

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

### **D 2 Definitions**

#### **Potential Hy's Law**

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

#### **Hy's Law**

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

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the

same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

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

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

- ALT  $\geq 3 \times$  ULN
- AST  $\geq 3 \times$  ULN
- TBL  $\geq 2 \times$  ULN

#### **Central Laboratories 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:

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

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

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

#### **If Local Laboratories Being Used:**

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

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

- Promptly enter the laboratory data into the laboratory eCRF

## D 4        Follow-up

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

If the participant does not meet PHL criteria, the investigator will:

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

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

If the participant does meet PHL criteria, the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within one day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change<sup>#</sup> in the participant's condition
- The Study Physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing), and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL lab kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available

<sup>#</sup>A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the Study Physician if there is any uncertainty.

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

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

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

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

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

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

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

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

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

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

## D 6        Laboratory Tests

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

### Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT (Gamma glutamyl transpeptidase) LDH Prothrombin time INR
Viral hepatitis	IgM (immunoglobulin M) anti-HAV HbsAg IgM and IgG (immunoglobulin G) anti-HBc  HBV DNA <sup>a</sup> IgG anti-HCV HCV RNA <sup>b</sup> 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) <sup>c</sup>
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin <sup>c</sup> Transferrin saturation

<sup>a</sup>HBV DNA is only recommended when IgG anti-HBc is positive

<sup>b</sup>HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive

<sup>c</sup>CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

## Appendix E Abbreviations

Abbreviation or special term	Explanation
ACE2	angiotensin-converting enzyme 2
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
AUC	area under the curve
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C <sub>max</sub>	maximum concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus 2019
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DILI	Drug Induced Liver Injury
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
EDC	electronic data capture
Fc	fragment crystallizable region
Fc $\gamma$ R	Fc gamma receptor(s)
FcRn	neonatal Fc receptor(s)
FTIH	first time in human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
HL	Hy's Law

Abbreviation or special term	Explanation
IB	Investigator's Brochure
IC <sub>50</sub>	50% maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
mAb	monoclonal antibody
MERS-CoV	Middle East respiratory syndrome coronavirus
NHP	Non-human primate
NOAEL	no-observed-adverse-effect level
NP	nasopharyngeal
OF	O'Brien Fleming
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PHL	Potential Hy's Law
PI	Principal investigator
PK	pharmacokinetic(s)
RBD	receptor binding domain
RNA	ribonucleic acid
RR	risk ratio
RRR	relative risk reduction
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SoA	Schedule of Activities
SpO <sub>2</sub>	oxygen saturation

Abbreviation or special term	Explanation
t <sub>1/2</sub>	terminal half-life
TBL	total bilirubin
TCR	tissue cross-reactivity
TM	triple mutation
ULN	upper limit of normal
VAERD	Vaccine-associated enhanced respiratory disease
WHO	World Health Organization
CCI	

## Appendix F WHO Clinical Progression Scale for COVID-19

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
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; 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	Dead	10

\*If hospitalized for isolation only, record status as for ambulatory patient.

ECMO Extracorporeal membrane oxygenation; FiO<sub>2</sub> Fraction of inspired oxygen; NIV Non-invasive ventilation; pO<sub>2</sub> Partial pressure of oxygen; SpO<sub>2</sub> Oxygen saturation.

Source: WHO Working Group 2020

Note: See also Appendix H for further guidance on the definition of hospitalization in this study.

## **Appendix G Participant-reported Symptom Diary**

Symptoms Associated with Covid-19

1. Record your temperature. If you take more than one temperature, record the highest one (i.e.,  
                 °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, eDiary 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

**eDiary 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, eDiary can be submitted.**

**If Yes, move to Question 4**

4. Have you needed to increase your supplemental oxygen intake?

- a. No
- b. Yes

## Appendix H Hospitalization Definition

Amid a rising number of coronavirus disease 2019 (COVID-19) hospitalizations across the world, leading to a shortage of hospital beds, temporary facilities are being utilized increasingly to manage severe COVID-19 patients who would have usually been treated in a traditional hospital setting.

Please note that in the TACKLE clinical study protocol, “hospitalization” is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

As hospitalizations are an integral component of both the primary and key secondary endpoints in the study, further guidance is provided regarding what constitutes these temporary facility or alternate care sites used for managing participants with severe COVID-19.

For the purposes of ascertaining an exclusion criterion or an endpoint event, individuals with severe COVID-19 will be considered “hospitalized” if they are

- 1 Managed in an alternative care site set up or authorized by states, provinces or equivalent jurisdictions or
- 2 Provided with acute hospital care at home meeting the criteria below
  - (a) Physician determines the patient’s condition as being appropriate for “acute in-patient hospitalization”
  - (b) Treating physician should have appropriate screening protocols before care at home begins, to assess both medical and non-medical factors, including patient’s preference, working utilities and assessment of physical barriers
  - (c) Patients are evaluated daily either in person or remotely by a qualified health care provider/treating physician, and are managed appropriately based on the patient’s treatment plan and local standards for COVID-19 management.

The appropriate WHO Clinical Progression Scale for COVID-19 score assigned to grade the participant’s condition would depend on the level of oxygen/ventilation support provided in these acute care settings.

## Appendix I Amendment History

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

<b>Version 6.0, 21 April 2021</b>
<b>Key amendment and rationale for change:</b>
<p>Amid a rising number of coronavirus disease 2019 (COVID-19) hospitalizations across the world, leading to a shortage of hospital beds, temporary facilities are being utilized increasingly to manage severe COVID-19 patients who would have usually been treated in a traditional hospital setting. As hospitalizations are an integral component of both the primary and key secondary endpoints in the study, further guidance is provided regarding what constitutes these temporary facility or alternate care sites used for managing participants with severe COVID-19.</p>
<p><b>Synopsis, Section 3 (Objectives and Endpoints), Section 4.2 (Scientific Rationale for Study Design), Section 5.2 (Exclusion Criteria), and new Appendix H (Hospitalization Definition):</b> To provide further guidance and clarity on the definition of hospitalization, and add a new endpoint reporting the type of hospitalization setting.</p>
<p><b>Section 8.2.4.1 (Females Only):</b> Removal of an inconsistency. Pregnancy tests should be performed as per the SoA.</p>
<p><b>Synopsis, Section 4.1 (Overall Design):</b> Clarification that high risk characteristics include current or former smoking.</p>
<p><b>Table 2 (SoA for Cohort 2):</b> Clarification that current or former smoking status should be recorded.</p>
<p>Other minor typographical corrections and change to Appendix order with the addition of the new Appendix.</p>

<b>Version 5.0, 31 March 2021</b>
<b>Key amendment and rationale for change:</b>
<p>Highly efficacious vaccines against SARS-CoV-2 are being deployed on a mass scale in the participating countries, leading to substantially decreasing attack rates for COVID-19 and reduced potential for study enrollment. Therefore, the interim analysis has been removed and the primary analysis adjusted so that it is completed 30 days after the 52<sup>nd</sup> event has</p>

occurred. This period, of 30 days, allows sufficient time for the 52<sup>nd</sup> event to be monitored, and any other events occurring during this time interval will also be evaluated. Enrollment will stop after the 52<sup>nd</sup> event has occurred.

Given recent efficacy results reported in treatment studies using other anti-SARS-CoV-2 monoclonal antibodies the standard of efficacy needed appears to be higher than those based on assumptions in place at the beginning of the pandemic, therefore, the sample size, the RRR and assumed incidence of severe COVID-19/death have been reassessed.

**Synopsis, Sections 1.2 (Schema), 4.1 (Overall Design), 9.4.1 (General Considerations), 9.5 (Interim Analysis), 9.4.2.1 (Primary Endpoint(s)), 9.6 (Data Safety Monitoring Board) and A5 (Committee Structure):** To reflect the change in primary analysis and resulting time change the interim analysis has been removed.

**Synopsis and Section 4.1 (Overall Design):** To improve participant enrollment the total number of sites has been changed from 'approximately 85 to 95 sites' to 'approximately 130 to 140 sites'.

**Synopsis, Sections 4.1 (Overall Design), 9.2 (Sample Size Determination):** As described above, sample size has been adjusted from "approximately" 1700 participants to "up to approximately" 1700 participants, and the 95% power to detect CCI [REDACTED]

**Synopsis, Sections 4.1 (Overall Design), 9.1 (Statistical Hypotheses), 9.4 (Statistical Analyses), 9.4.1 (General Considerations), 9.4.2.1 (Primary Endpoint(s)), Section 9.4.5 (Methods for Multiple Testing Control):** As described above, the primary analysis has been changed from '90 primary endpoint events' to '30 days after the 52<sup>nd</sup> primary endpoint event'. Furthermore, enrollment will stop after the 52<sup>nd</sup> event has occurred.

**Synopsis, Sections 4.1 (Overall Design) and 6.3.1 (Randomization):** In order to ensure the high-risk proportion of participants of more than 60% is reached enrollment of low-risk participants has stopped. To make this clear, the statement 'The enrollment of low-risk participants has stopped' has been added to the CSP.

**Table 1 (Schedule of Activities for Cohort 2) and Table 2 (Schedule of Activities for Cohort 2):** Due to the overlap in visit windows for Day 6 and Day 8 a note has been added that these assessments must be performed on different days. According to the exploratory endpoints, the household infection report is only required through Day 169, and therefore, its collection has been removed from Day 366.

**Section 8.2.4 (Clinical Safety Laboratory Assessments):** Text added to confirm that sites

may use local laboratories for safety laboratory assessments only if COVID-19 restrictions limit their ability to use the central laboratory.

**Section 9.4.2.2 (Secondary Endpoint(s)):** Confidence interval changed to 95% and the null hypothesis tested at 5%. This change corresponds to the change in the methodology used for the control of multiple testing, which is now a hierarchical testing strategy.

**Section 9.4.7 (Subgroup Analyses):** Efficacy in relation to viral variants has been added as a possible analysis.

#### **Version 4.0, 10 March 2021**

##### **Key amendment and rationale for change:**

Pregnant women and breastfeeding mothers are excluded from the trial (Criterion 16) as there is insufficient data on the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes or effects of the drug on the breastfed infant, or on milk production. All women of child bearing potential must have a negative pregnancy test result at Visit 1 (Criterion 8b). AstraZeneca acknowledges the risk for severe COVID-19 in pregnant women but would like to establish the risk/benefit profile in adults before including pregnant women in the clinical trial.

**Synopsis, Sections 4.1 (Overall Design):** Pregnancy has been removed from the list of high-risk identifiers.

**Sections 5.1 (Inclusion Criteria), 8.3.10 (Pregnancy), 8.3.10.1 (Maternal Exposure), Table 1 (Schedule of Activities for Cohort 1), Table 2 (Schedule of Activities for Cohort 2):** Instructions added that women must have a negative pregnancy test before dosing and that IMP should not be given to pregnant women. Any pregnancies discovered before a participant has received IMP do not need to be reported.

**Section 5.2 (Exclusion Criteria):** The following exclusion criterion has been added ‘16. For women only, currently pregnant (confirmed with positive pregnancy test) or breast feeding’;.

**Section 8 (Study Assessments and Procedures):** To reflect confirmed blood volumes for study assessments the maximum amount of blood collected has been changed from 250 mL to 300 mL.

**Version 3.0, 26 February 2021**

**Key amendment and rationale for change:**

COVID places pregnant women at increased risk of poor outcomes and poor pregnancy outcomes (CDC 2021). A fetal TCR study showed no binding of AZD7442 mAbs to any fetal tissues tested. Prior experience with antibody therapy against infectious diseases and with other mAbs suggests low-risk in pregnancy. Therefore, the exclusion of pregnant or breast feeding women has been removed from the CSP.

To provide data on AZD7442 for 5 half-lives the study has been extended to 15 months allowing a safety assessment and an optional serum sample for PK, ADA, and CCI to be added at Day 457. Study endpoints have been adjusted accordingly.

In response to a health authority request to use a different statistical approach to alpha-spending for the proposed efficacy analyses, the boundaries for the interim analysis and primary analysis have been changed.

Instructions have been added to confirm that participants may receive investigational agents for COVID-19, if required, and per local health authority guidance.

Clarifications to other sections have been made to avoid confusion at study sites.

**Synopsis, Sections 1.2 (Schema), 3 (Objectives and Endpoints), 4.1 (Overall Design), 4.2 (Scientific Rationale for Study Design), 6.1.1 (Investigational Medicinal Products), 9.4 (Statistical Analysis), 9.4.1 (General Considerations), 9.4.3.1 (Primary Endpoint(s)), Table 1 (Schedule of Activities for Cohort 1) and Table 2 (Schedule of Activities for Cohort 2):** To provide safety and PK assessments after 5 half-lives the study has been extended from last visit on Day 366 to last visit on Day 457. Endpoints for safety and CCI have been adjusted to reflect this additional time point.

**Synopsis, Section 4.1 (Overall Design):** To avoid confusion at study sites, language has been added to confirm that 'Day 1' of symptoms means the first day symptoms emerge.

To align with the CDC and to clarify the classification of high-risk participants, pregnancy and smoking have been added as high-risk identifiers. Pregnancy had previously been omitted because pregnant women were excluded from the CSP, however, they are now included. The addition of smoking reflects that smoking status is already collected at baseline.

**Synopsis, Section 9.2 (Sample Size Determination):** To implement a more rigorous approach to stopping boundaries, the sample size determination has been changed from a Pocock boundary to an O'Brien-Fleming alpha spending function for the interim and

primary analysis.

**Table 1 (Schedule of Activities for Cohort 1) and Table 2 (Schedule of Activities for Cohort 2):** Footnote updated to clarify that COVID-19 related symptoms should be collected pre- and post-dose on Day 1.

To ensure the correct assessment is performed, rows labelled ‘ECG’ have been changed to ‘Triplicate 12-lead ECG’. The Remote visit has been defined as either a phone call or a web-based virtual assessment.

To the symptom diary entry, the following footnote has been added: ‘If Day 29 visit is conducted earlier in  $\pm$  4 day window, participant should retain symptom diary in order to complete required daily entries through Study Day 29’.

**Table 2 (Schedule of Activities for Cohort 2):** A footnote has been added to the IMP administration to describe required safety monitoring. This had been previously omitted from the CSP text.

**Sections 4.1 (Overall Design), 5.1 (Inclusion Criteria), 5.2 (Exclusion Criteria), 8.3.10 (Pregnancy), 8.3.10.1 (Maternal Exposure), Table 1 (Schedule of Activities for Cohort 1) and Table 2 (Schedule of Activities for Cohort 2):** Based on the low-risk to pregnant or breast feeding women and the potential benefit pregnant women may receive from mAb treatment the exclusion Criterion 16, excluding pregnant and breast feeding women has been removed and inclusion Criterion 8(b) has been amended to remove the requirement for a negative pregnancy test. Pregnancy has also been added to the list of high-risk factors that can lead to progression to severe COVID-19.

**Section 5.1 (Inclusion Criteria):** In response to health authority feedback recommending that a minimum score of  $> 0$  on the clinical progression scale is not appropriate, Criterion 3 has been changed from ‘WHO Clinical Progression Scale score  $> 0$  and  $< 4$ ’ to ‘WHO Clinical Progression Scale score  $> 1$  and  $< 4$ ’.

**Section 5.1 (Inclusion Criteria):** To Criterion 4, the equivalent Fahrenheit temperature has been added alongside Celsius.

**Section 5.1 (Inclusion Criteria):** To Criterion 8(a), condom use for male participants has been changed from ‘365 days following administration of IMP’ to ‘90 days following administration of IMP’. As the mAbs have no human target and fetal TCR studies showed no mAb presence the risk of transmission is low, and therefore the number of days has been reduced to reflect approximately 1 half-life.

**Section 5.2 (Exclusion Criteria):** To ensure that individuals likely to receive a vaccine

during their country's immediate roll out are not included in the study, Criterion 4 changed from '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' to '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 administration immediately after enrollment'.

**Section 5.2 (Exclusion Criteria):** Criterion 5 language clarified: 'requirement for mechanical ventilation' changed to 'current requirement for mechanical ventilation'.

**Table 5 (Summary of Permitted, Prohibited, or Restricted Medications):** To avoid confusion at study sites, the table has been updated with the following clarifications:

- Allergen immunotherapy should be allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Day 1 and there is no anticipated change during the treatment period. Non-prescription treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted.
- To ensure participants who become ill with COVID-19 receive all possible treatments available to them, no restrictions to these treatments are included in the study. Instructions have been added to confirm that participants hospitalized with COVID-19 may receive investigational agents under emergency use authorization or equivalent regulations if available.
- Blood/plasma donation is restricted for one-year.

**Section 8.1.6 (Household Infection Report):** Clarification to text that all members of a participant's household should be considered for the infection report.

**Section 8.2.1 (Physical Examination):** To ensure the correct recording and implementation of the targeted physical examination, the text has been updated to confirm that where no new complaints or findings are observed this should be documented. Abnormal clinical findings after randomization should be reported per the AE and SAE reporting guidelines within the CSP.

**Sections 6.5 (Concomitant Therapy) and 8.3.10.1 (Maternal Exposure):** In response to health authority comments and for the safety of participants, restriction on ova donation for at least 365 days after IMP dosing has been added.

**Sections 6.5 (Concomitant Therapy) and 8.3.10.2 (Paternal Exposure):** In response to health authority comments and for the safety of participants, restriction on sperm donation for at least 365 days after IMP dosing has been added.

**Section 9.3 (Populations for Analyses):** To correct a mistake in the previous CSP, the Virology analysis set has been corrected to include participants who have received treatment instead of only those randomized.

**Section 9.4.2.2 (Secondary Endpoint(s)):** Key secondary endpoint language clarified; no changes to the planned analysis for the key secondary endpoint were made.

**Section 9.4.5 (Methods for Multiple Testing Control):** To implement a more rigorous approach to stopping boundaries, the multiple testing control has been updated to O'Brien Fleming alpha spending function.

**Appendix B (Adverse Events: Definitions and Procedures for Recording Evaluating, Follow-up, and Reporting):** To correct an error and avoid confusion, the Severity Rating Scale in Appendix B has been updated to match the scale cited in the main body and implemented in the CRF.

**Appendix G (Participant-reported Symptom Diary):** The diary was previously published separately from the CSP, however, the symptom diary has now been included within the CSP so that they can be published as one document.

Corrected typos are not listed above.

## Version 2.0, 22 December 2020

### Key amendment and rationale for change:

**Synopsis, Section 3 (Objectives), and Section 9.4.2.2 (Secondary Endpoint):** Update to the key secondary objective and associated analysis estimand to include as intercurrent events, participants who are unblinded to be considered for COVID-19 vaccination. Consequential consistency change to Section 9.4.2.1 (Primary Endpoint).

**Synopsis, Table 1 (Schedule of Activities) footnote, Section 4.1 (Overall Design), and Section 8.2.5.1 (Monitoring after IMP Administration):** Addition of text ensuring dosing of participants in the sentinel groups is staggered.

**Section 6.3.2 (Blinding):** Addition of sentence to include the potential need for unblinding in the event of a participant considering COVID-19 vaccination.

**Section 6.5 (Concomitant Therapy) and Section 6.5.1 (COVID-19 Vaccination):** Modification to instructions in how to handle COVID-19 vaccination, to provide greater

clarity to Investigators.

Corrected typos are not listed above.

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