A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (Trial H4: AZD7442)

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Appendix H4: AZD7442 – version 2.0 (09 April 2021)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between *AstraZeneca* and NIAID in relation to the TICO/ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.4.1. Introduction and rationale for studying the agent

AZD8895 and AZD1061, known collectively as AZD7442, are two fully human neutralizing immunoglobulin G (IgG)-1 kappa monoclonal antibodies (mAb) that target two distinct epitopes on the receptor-binding domain of the spike protein of SARS-CoV-2 [1]. They neutralize SARS-CoV-2 in live virus assays, preventing viral entry into human cells and subsequent viral replication [1]. This mechanism is expected to result in a clinically important decrease in viral replication, mitigating the severity of disease in patients in whom ongoing viral replication is an important driver of COVID-19 pathophysiology.

AstraZeneca (AZ) is a global, science-led biopharmaceutical business. Its innovative medicines are used by millions of patients worldwide. AZD7442 is made by AstraZeneca. The two monoclonal antibodies of which it is comprised were derived from B cells isolated from people who recovered from SARS-CoV-2 infection [1]. Out of hundreds of anti-SARS-CoV2 antibodies that were screened, these two monoclonal antibodies were selected for affinity to SARS-CoV-2 spike protein domains, neutralization potency, and their developability. They were subsequently modified by two sets of triple amino acid substitutions in their Fc regions, TM (L234F/L235E/P331S), intended to diminish blinding to cellular Fc receptors, and YTE (M252Y/S254T/T256E), intended to prolong their elimination half-lives [1]

Whereas one antiviral agent (remdesivir) has been demonstrated to have clinical benefit in the target population for this trial and is now part of standard-of-care (see Appendix I), it is plausible that additional antiviral effects from the combination of AZD8895 and AZD1061 together with remdesivir may provide additive, if not synergistic, antiviral effects and hence, contribute to improvement of time to sustained recovery.

AstraZeneca is evaluating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD7442 in 60 volunteers, in a randomized, placebo-controlled, single-ascending-dose, Phase 1, first in human study (Study D8850C00001; NCT04507256)) [2]. This study is ongoing and preliminary safety, tolerability, PK and PD data from these may inform the dose level administered in this study.

H4.1.1 *Potential risk and benefits from AZD7442*

Anticipated risk is considered low, based on the known mechanism of action for human-derived neutralizing antibodies against viral proteins in acute viral disease states [3, 4]. AZD7442 is comprised of two highly specific mAbs directed at viral epitope(s) not found in healthy humans. The complementarity determining regions (CDRs) of AZD8895 and

AZD1061 are identical to the parent mAbs derived from B lymphocytes of naturally convalescent SARS-CoV-2-infected patients [1]. In the Fc domain of both mAbs, three amino acids were substituted (YTE; M252Y/S254T/T256E) to extend the half-life of the antibodies to approximately 80 days by increasing binding to FcRn [5, 6]. As the antibodies target viral epitopes, off-target binding is considered unlikely, and this expectation was confirmed by the absence of AZD7442-binding to human and cynomolgus monkey tissues in a tissue cross-reactivity study [7].

AZD7442 is comprised of two antibodies (AZD8895 and AZD1061) which neutralize SARS-CoV-2 by binding to unique, non-overlapping epitopes on the RBD of the viral spike protein, which is responsible for receptor binding and cellular fusion. Both AZD8895 and AZD1061 bind the RBD with nanomolar affinity and are individually capable of sterically blocking the virus from engaging its cellular receptor, hACE2. In both IgG and Fab formats, AZD8895 and AZD1061 were individually capable of blocking SARS-CoV-2 spike RBD binding to hACE2 in competition binding assays [7] . Furthermore, the two antibodies demonstrate concurrent binding to RBD on the SARS-CoV-2 spike protein, as evidenced by both binding competition assays and electron microscopy images showing both Fabs bound simultaneously [1, 7]. Whereas AZD8895 binds the open conformation of the spike protein, which exposes the residues that mediate ACE2 interaction, AZD1061 binds to both the open and the closed conformation [1] This binding translates to potent neutralization of SARS-CoV-2 infection by AZD7442 in microneutralization assays and focus reduction neutralization tests, with IC_{50} values between 10 to 26 ng/mL [7]. The two mAbs also demonstrate potent neutralization of SARS-CoV-2 and pseudovirus in vitro [1, 7]. The parental versions of AZD8895 (COV2-2196) and AZD1061 (COV2-2130) provided protection from SARS-CoV-2 infection in several in vivo models, including mice and non-human primates [1]. These mAbs reduced viral load in the lungs of animals, whether administered prophylactically or up to 12 hours after virus infection. The reduction in viral load corresponded to reduced alveolar damage and inflammation in the lungs of infected animals. AZD7442 was additionally evaluated in rhesus macaques in both prophylactic and treatment settings. Intravenous administration of 4 mg/kg or 40 mg/kg AZD7442 resulted in expected mAb concentrations in the serum that provided peak neutralizing antibody titers that ranged from 50,000 to 1,768,000 and prevented replication of SARS-CoV-2 in the nasal mucosae and lungs of infected animals [7]. AZD7442 administration 24 hours after infection limited replication of SARS-CoV-2 such that viral replicating RNA was only detected up to 4 days post-infection as compared to 8 days post-infection in infected animals that received isotype control mAb [7].Collectively, these data demonstrate that the mAbs that comprise AZD7442 potently neutralize SARS-CoV-2 in vitro and are efficacious in animal challenge models when administered prophylactically or therapeutically.

Potential risks for infusion of an IgG1 mAb directed towards a microbial pathogen are mostly associated with either infusion-related immediate and non-immediate hypersensitivity reactions, or infusion-related cytokine release syndrome. Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to: anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticarial, tachycardia, and throat irritation or chest

tightness. Additional signs and symptoms associated with cytokine release syndrome may also include fever, headache, myalgia, nausea, and vomiting.

The single infusion in this study will be administered at a controlled rate, the study participants will be monitored closely, and adjustments in the infusion rate will be made and/or the infusion paused or stopped as well as any supportive measures instituted as per local practice, if indicated.

The pathophysiology for SARS-CoV-2 is not well understood. Reports of fatal acute respiratory disease with uncontrolled pulmonary inflammation and increased secretion of proinflammatory cytokines is suggestive of a cytokine storm, especially in patients who are critically ill [8-10]. These reports have led to the speculation that SARS-CoV-2 may bear some resemblance to SARS-CoV and MERS-CoV, which have been associated with reports of antibody-mediated enhancement (ADE) of disease in some in vivo models that was attributed to Fc receptor-mediated uptake of virus-antibody complexes into cells such as alveolar macrophages, resulting in an overstimulation of the host immune response [11-18]. To date, there is no evidence of ADE of disease associated with COVID-19 in humans, although it remains a theoretical risk that is being closely monitored. Additionally, limited experience with the use of convalescent serum as a treatment for patients with severe COVID-19 has not indicated safety concerns [19]. To reduce the theoretical risk of antibody-dependent enhancement of disease (ADE; see below), three additional amino acid substitutions (TM; L234F/L235E/P331S) were incorporated in the Fc domain of both mAbs, which reduces their binding to Fc gamma receptors (FcγR) and complement proteins and thereby reducing effector functions [20]. The TM substitutions have been used in several other AstraZeneca mAb programs in oncology and autoimmune diseases that have been studied in the clinic; all have shown an acceptable safety profile [21, 22].

The non-clinical safety program includes: 1) a GLP-compliant tissue cross reactivity (TCR) study assessing AZD7442 binding to a panel of 32 human and cynomolgus monkey tissues and 2) a GLP-compliant, single-dose toxicology study in cynomolgus monkeys of 8 weeks duration with 2- and 8-week follow up. Data from the complete GLP TCR study demonstrated that no binding was observed to any of the human or cynomolgus tissues tested. In the GLP toxicology study, administration of AZD7442 via IV infusion or IM injection was well tolerated in cynomolgus monkeys at a dose level of 600 mg/kg (combination of 300 mg/kg of AZD8895 and 300 mg/kg of AZD1061) and 150 mg/kg (75 mg/kg of each antibody), respectively. In the 2-week and 8-week phases of the GLP toxicology study there were no AZD7442-related adverse changes in any endpoint examined including safety pharmacology endpoints like ECG, BP, HR and BT and assessments of CNS and respiratory endpoints. The doses of 600 mg/kg IV and 150 mg/kg IM are considered the single dose No Observed Adverse Event Levels (NOAELs). Together, the lack of binding to any tissues in the GLP TCR study and the tolerability in the single dose tox study support the safety of the proposed clinical plans for AZD7442.

The first in humans Phase 1 study of AZD7442 enrolled 60 subjects, randomized 5:1, AZD7442:placebo, in a single-ascending dose study of 5 equal cohorts that assessed AZD7442 doses of 300 mg IM (150 mg of AZD8895 and 150 mg of AZD1061 administered as separate intramuscular injections), 300 mg IV (150 mg of AZD8895 and

150 mg of AZD1061 administered as separate sequential IV infusions), 1000 mg IV (500 mg of AZD8895 and 500 mg of AZD1061 administered as separate sequential IV infusions), 3000 mg IV (1500 mg of AZD8895 and 1500 mg of AZD1061 administered as separate sequential IV infusions), and 3000 mg IV (1500 mg of AZD8895 and 1500 mg of AZD1061 co-administered as a mixed IV infusions). The second interim analysis, reporting cumulative data after the last subject dosed had completed 7 days post-dose, identified no serious adverse events, no adverse events of greater than mild to moderate severity, no hypersensitivity reactions, no injection site reactions, no infusion reactions, and no imbalance between the placebo and active treatment arms.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of AZD7442 may be found in the Investigator's Brochure, Participant Information Leaflet, and/or Development Safety Update Report.

Given the data on AZD7442 from the on-going Phase 1 study [2, 7], the well-described safety profile of other therapeutic human monoclonal antibodies with foreign (non-human) targets, and the limited disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment of this study is considered favorable.

H4.1.2 *Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)*
The ACTIV-2/3 Agent Selection Committee (ASC) reviewed the AstraZeneca (AZ) SARS-CoV-2 neutralizing antibody cocktail AZD7442 (AZD8895 & AZD1061) and voted in favor of the agent proceeding into ACTIV-2 and ACTIV-3, and the TOC endorsed that recommendation. AZ's AZD7442 cocktail was supported because AZ presented detailed epitope binding data (e.g., negative stained electron microscopy); robust preclinical supporting data (e.g., PK, tolerability, efficacy); and detailed information about Fc modifications and their likely effects. For preclinical data for viral neutralization, live virus neutralization against the original Washington strain of SARS-CoV-2 showed [USA-WA1/2020, AZD8895] 9/NA | 32/NA ng/mL, [USA-WA1/2020, AZD1061] 32/NA | 115/NA ng/mL, and [USA-WA1/2020, AZD7442] 10/NA | 26/NA ng/mL for the individual antibodies and the cocktail, respectively. For viral binding, AZ showed that their antibodies bound to S protein RBD - AZD1061: K444, G447 and AZD8895: F486, N487 with strong affinity RBD, AZD8895/1061]: 2.15E-9/2.18E-9 M and [Spike trimer, AZD8895/1061]: 3.41E-9/5.29E-9 M. This was particularly important because the ASC initially approved the AZ cocktail to move forward while the tissue cross reactivity studies were still in process. These assays in humans and non-human primates have since read out negative. AZD7442 also showed excellent in vivo preclinical efficacy in mice and non-human primates.

Both AZ antibodies are human neutralizing immunoglobulin G1 that bind distinct epitopes in receptor binding domain (RBD) in spike protein of SARS-CoV-2 virus. They are both YTE (M257Y, S259T, T261E) & TM FcGR (L234F, L235E, P331S) modified isoforms of monoclonal antibodies. While the YTE modification improves the half-life of antibodies to provide prolonged duration of protection and extended therapeutic treatment window,

the TM modification reduces binding activity to human Fc receptors, thereby minimizing the potential risk of Fc-mediated antibody-dependent enhancement.

In addition, the ASC appreciated that AZ had already filed their pre-submission for Investigational New Drug (IND) and was targeting filing for its full IND in early September. AZ's Phase I study was targeted be complete by mid-October, with the candidate agent ready to enter ACTIV clinical trials by late November pending Phase I results. While it was the second neutralizing antibody cocktail selected for the ACTIV trials, AZD7442 did have slightly different binding sites and Fc modifications for its antibodies that the ASC considered to be of value to study against the other agents already selected for the trial. Finally, the ASC found the manufacturing and scalability strategy for AZ sufficient for the full trial and beyond.

AstraZeneca's medicines are used worldwide. AstraZeneca has stated that generally their intent is to pursue licensure in countries where pivotal trials are conducted. In the case of the COVID-19 pandemic, the actual decision to pursue licensure will be impacted by other factors which may include: status of the COVID pandemic in the country and medical need, availability of other therapies including vaccines, available drug supply and other supply feasibility issues, and other regulatory considerations.

H4.1.3 Justification for dose chosen for AZD7442

Human efficacious doses for AZD7442 were evaluated using in vitro potency data (virus neutralizing activity of AZD7442 against SARS-CoV-2) and PK data. In addition, a viral-dynamic model was developed to understand the pharmacodynamic effects of AZD7442 inhibiting a SARS-CoV-2 infection and the resulting immune response. In the viral-dynamic model the AZD7442 partition ratio between lung epithelial lining fluid -to-serum is assumed as 1% and the potency (IC80; inhibiting SARS-CoV-2 by 80%) as 40 ng/mL. With the dose of 600 mg IV predicted to result in exposures in the ELF that exceed the IC80, this dose when administered before the time of peak viral load (~ 7 days after day of infection) is expected to result in reduction of the peak viral load and earlier eradication of the viral load. When administered after the peak viral load has been reached, AZD7442 is still expected to result in earlier viral load eradication compared to when drug is not present.

IV was selected over IM as the administration route for this treatment study because peak concentrations are achieved immediately after IV administration while it takes > 7 days after IM injection to achieve peak concentrations and early treatment is critical for this patient population. Also, the peak concentrations following IV infusion are about two times higher than following IM injection at the same dose level and higher C_{max} may be correlated with better efficacy. The available observed AZD7442 concentration data over the first 60 days in Phase 1 study D8850C00001 is shown in Figure 1 below.

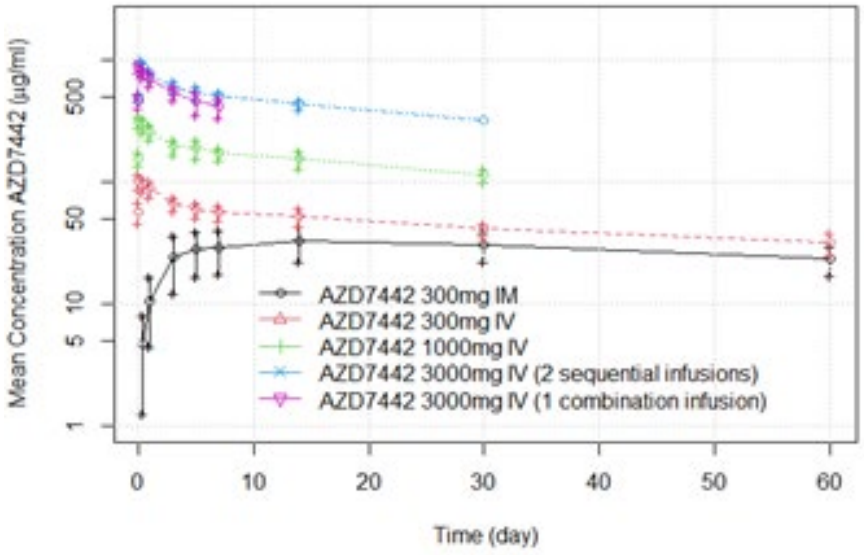

Figure 1: Mean (SD) Serum AZD7442 concentration over time in Phase 1 Study D8850C00001 in healthy volunteers

Based on the above justifications and the available safety data, the following dose of AZD7442 has been chosen for study in ACTIV-3: 600 mg IV (equating to 300 mg AZD8895 + 300 mg AZD1061).There are no significant safety concerns about using the 600 mg dose of AZD7442, as side effects in antibody therapy are not generally dose-dependent and doses higher than this dose has been tested in the Phase 1 study to confirm the safety.

H4.2. Agent specific eligibility criteria

In addition to the inclusion and exclusion criteria outlined in the master protocol, the following patients will be **excluded**:

1. pregnant women
2. nursing mothers
3. women of child-bearing potential who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with men or practice appropriate contraception through the entire 18 months of the study
4. men who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception through the entire 18 months of the study.

No other specific inclusion or exclusion criteria need to be altered.

In addition, prior to the initial futility assessment which is performed when approximately 150 participants have been enrolled on AZD7442 and 150 on placebo, patients on high-flow oxygen or non-invasive ventilation (category 5 of the pulmonary ordinal outcome) will be excluded. These patients may be eligible for the trial if the initial futility assessment is passed by this agent.

H4.3. Description of investigational agent

H4.3.1. Administration and duration

See the PIM and Pharmacy Procedures for details. See also section H4.5 below for guidance on the clinical management of the infusion, including infusion-related reactions.

The infusion rate may be reduced as deemed necessary, if an infusion reaction is observed. Participants will be closely monitored during the infusion and every 30 minutes for at least 2 hours after completion of the infusion. Additional monitoring may be necessary based on clinical judgement of the study investigator(s) and/or site staff, and in accordance with the master protocol. The site must have resuscitation equipment, emergency drugs and appropriately trained staff available during the infusion and for at least 2 hours after the completion of the infusion.

If a participant has not already received the relevant dose of remdesivir at the day of enrolment, and has no contraindications to start remdesivir, it is recommended (but not required) that the relevant dose of remdesivir is infused after the infusion of AZD7442/ placebo is completed.

H4.3.2. Formulation and preparation

AZD7442 (AZD8895 and AZD1061) is provided in separate vials containing 1.5 mL solution each containing 150 mg of AZD8895 or 150 mg of AZD1061. AZD7442 (AZD8895 and AZD1061) must be stored between 2ºC and 8ºC.

A total of 2 vials of AZD88995 and two vials of AZD1061 are required for the dosing of the solution at 600 mg (see Table H4.1). Placebo is normal saline from local supply. Detailed instructions for preparing the infusion bag for the investigational agent are described in the pharmacy procedures for this agent.

The master protocol, general procedures described in the PIM, and pharmacy procedures for preparing and dispensing the infusion by the unblinded pharmacist will be followed.

Table H4.1. Study medication overview.

Intervention Name	**Placebo**	**AZD7442**
Dose Formulation	0.9% (w/v) saline	AZD8895: single-use vial (100 mg/mL) AZD1061: single-use vial (100 mg/mL)
Dosage Level(s) (mg)	Not applicable	600 mg dose (300 mg AZD8895 and 300 mg AZD1061)

Dose Volume (mL)	Refer to pharmacy procedures	Refer to pharmacy procedures
Route of administration	IV infusion	IV infusion
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Commercially available 0.9% (w/v) saline	AstraZeneca
Packaging and Labeling	Commercially available 0.9% (w/v) saline	Study Intervention will be provided in single-use 10R vials, individually packaged in a carton, and labeled appropriately

H4.3.3 Supply, distribution, and accountability

Procedures for ordering and accepting drug, for maintaining inventory of AZD7442 (AZD8895 and AZD1061), and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H4.3.4. Contraindicated medications

No medication is known to be contraindicated in patients receiving the investigational agent. Whenever a concomitant medication or the study agent is initiated or a dose changed, investigators must review the concomitant medication's prescribing information and the relevant protocol appendix/appendices, as well as the most recent package insert, Investigator's Brochure, or updated information from DCR, NIAID to obtain the most current information on drug interactions, contraindications, and precautions.

H4.3.5. Precautionary medications

The clinical site should have necessary equipment and medications for the management of any infusion reaction (see section H4.5 below).

Premedication for infusions is not planned.

The investigators and sponsor may decide to recommend premedication, if the frequency of infusion reactions among participants warrants it. If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation. Any premedication given will be documented as a concomitant therapy.

H4.4. Clinical and laboratory evaluations

H4.4.1 Timing of Assessments

Appendix B outlines the clinical and laboratory monitoring. Assessment and reporting of AEs (section 10.1.1), SAEs (section 10.1.2) and unanticipated problems (section 10.1.3) and their severity, causality (section 10.1.5) and expectedness (section 10.1.6) is performed as outlined in the relevant section of the master protocol.

H4.4.2 Immunogenicity Assessments

At the visits specified in the master protocol (Days 0, 28, and 90) venous blood samples will be collected to determine antibody production against AZD7442. Serum samples for determination of ADA will be tested at PPD Inc. on behalf of AstraZeneca, using a validated assay. Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination. Remaining volume from the PK sample may also be used for immunogenicity assessments as needed.

H4.4.3. Pharmacokinetic Assessments

At the visits specified in the master protocol (Days 0, 5, 28, and 90) venous blood samples will be collected to determine AZD7442 serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2 mL of the serum collected, as described in the Master Protocol Appendix B as "Research Sample Storage". PK samples may be assessed by a validated assay at a bioanalytical lab. The PK assessment will use the same 2 ml serum aliquot specified in the Immunogenicity assessment section above (H4.4.2). Analysis of samples from placebo-treated subjects is not planned. Remaining sample used for PK may be pooled and used for exploratory metabolism, pharmacodynamic, virologic, or bioanalytical method experiments as deemed appropriate.

H4.5. Clinical management issues

All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

H4.5.1. Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions' severity will be assessed and reported using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 (July 2017) [23].

H4.5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (adrenaline), acetaminophen (paracetamol) and antihistamine.

The pharmacy will be provided with labels to be placed on the IV bag before dispensing (refer to the Pharmacy Procedures).

The pharmacy is required to provide 0.9% (w/v) saline and IV bags, similarly shrouded.

H4.5.3. Management of Infusion Reactions including Discontinuation

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life-threatening infusion reaction occurs with AZD7442/placebo, its use should be permanently discontinued.

If a participant is not infused with AZD744/placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in the master protocol (Appendix B for overview), should be adhered to as indicated.

H4.5.4. Adverse Events of Special Interest (AESI)

The following are AESIs for the agent AZD7442 or placebo for AZD7442:

- Infusion-related reactions
- Allergic/hypersensitivity reactions

H4.5.5. Incident Pregnancy in Participants or Their Partners

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

The participant will then be followed to determine the outcome of the pregnancy and reported on the Pregnancy Outcome eCRF.

If an investigator learns that a male participant's partner has become pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its outcome, after obtaining consent from the pregnant partner. The outcome of the pregnancy will be reported on the Pregnancy Outcome eCRF.

H4.6. References

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