Interim Clinical Study Report Synopsis	
Drug Substance	AZD7442
Study Code	D8851C00001
Edition Number	Final
Date	31 May 2022
EudraCT Number	2020-005315-44
NCT Number	NCT04723394

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

Interim Report Synopsis

Study Dates:

First participant randomized: 29 January 2021

Last participant last visit: ongoing

- The Primary Efficacy analyses are based on a Data Cut-off of 21 August 2021 and a Database Lock of 28 September 2021
- The key secondary efficacy analyses, PK, PD and safety are based on a Data Cut-off of 14 January 2022 and a Database Lock of 18 February 2022

Phase of Development: Phase III

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2 SYNOPSIS

Interim Report

This report includes 2 data cut-offs (DCOs), the Primary DCO (21 August 2021) up to Day 29 and the Key Secondary DCO (14 January 2022) up to Day 169. In addition to the primary analysis performed at the Primary DCO, the repeated analyses at the Key Secondary DCO are presented for primary and secondary endpoints, the key secondary endpoint is also presented. Pharmacokinetic (PK), pharmacodynamic (PD), and safety data are summarized for the Key Secondary DCO.

Study Centers

Participants were randomized at 95 participating sites in 14 countries.

Publications

None at the time of writing this report

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objective	Estimand Description/Endpoint
Primary	
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.	**Population:** Modified full analysis set.
	Endpoint: A composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 was characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (SpO_2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher
	Intercurrent events: The set of intercurrent events for this estimand consisted of receipt of COVID-19 treatment product prior to Day 29 without already having met the primary efficacy endpoint. The set of intercurrent events was to be handled following the treatment policy strategy.
	Summary measure: 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).
To evaluate safety and tolerability of a single IM dose of AZD7442 compared to placebo.	AEs, SAEs, and AESIs through end of study.
Key Secondary	
	Population: Modified full analysis set.

Table S1 Objectives and Endpoints

Objective	Estimand Description/Endpoint
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either death or hospitalization [a] for COVID-19 complications or sequelae through Day 169.	**Endpoint:** A composite of either death from any cause or hospitalization [a] for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169). First reported in this CSR.
	Intercurrent events: The set of intercurrent events for this estimand consisted 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 was to be handled following the treatment policy strategy.
Other Secondary	
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 2021 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 was 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.	• Time to return to usual (pre-COVID-19) health through Day 29. • 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.
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 [redacted]	
CCI [redacted]	[redacted]

Table S1 Objectives and Endpoints

Objective	Estimand Description/Endpoint
CCI	

Table S1 Objectives and Endpoints

Objective	Estimand Description/Endpoint
CCI [redacted]	[redacted]
[redacted]	[redacted]

[a] Hospitalization was 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, CSP for further guidance on the definition of hospitalization.

Ashraf-Kashani and Kumar 2017, Ashraf-Kashani N, Kumar R. High-flow nasal oxygen therapy. BJA Education 2017;17(2):57 62.

Sharma et al 2021, Sharma S, Danckers M, SanghaviD, Chakraborty RK. High Flow Nasal Cannula. In: StatPearls [Internet] Treasure Island (FL). StatPearls Publishing; 2021 Jan-PMID:30252327.

Only data available at the time of the Primary and Key Secondary DCOs are presented.

ADA, anti-drug-antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CSP, clinical study protocol; CSR, clinical study report; DCO, data cut-off; ECMO, extracorporeal membrane oxygenation; CCI [redacted] ICU, intensive care unit; IM, intramuscular; CCI [redacted] PK, pharmacokinetic; RNA, ribonucleic acid; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation; WHO, World Health Organization.

Study Design

This is an ongoing, Phase III, randomized, double-blind, placebo-controlled, multi-country, multicenter study assessing the safety and efficacy of a single intramuscular (IM) 600 mg dose of AZD7442 compared to placebo for the treatment of coronavirus disease 2019 (COVID-19).

During the study, all participants received background local standard of care therapy (according to participating institution/hospital) regardless of the study treatment group to which they are randomized.

Randomization was stratified (using centralized blocked randomization) by:

1 Time from symptom onset (≤ 5 days versus > 5 days)
2 High-risk versus low-risk of progression to severe COVID-19

The first 20 participants dosed (approximately 10 planned for the AZD7442 group and 10 planned for the placebo) formed a sentinel group.

Participants were enrolled into one of 2 independent cohorts:

- Cohort 1 (n = approximately 300), which included the sentinel group, underwent 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) to 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 received a single dose of investigational medicinal product (IMP). The dose was administered as 2 separate IM injections (one for AZD8895 and one for AZD1061) in the gluteal region. In Cohort 1, the first 20 participants dosed (ie, the sentinel group) underwent safety monitoring for 4 hours post-IMP administration before further participants were dosed. At each site, there was an interval of 24 hours after dosing of the first participant in the sentinel group before the next participant could be dosed. The next 80 participants (21 to 100) underwent safety monitoring for 2 hours post-IMP administration. If hypersensitivity reactions were observed in the first 100 participants, subsequent participants continued to be monitored for 2 hours post-IMP administration, otherwise the minimum safety monitoring time was 1 hour. In addition, the sentinel group was contacted daily (in-person or by telephone) for the first 4 days after IMP administration.

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

The study was completely double-blind until the primary analysis. At the time of primary analysis, pre-specified Sponsor and Clinical Research Organization personnel were unblinded for primary read-out. The site personnel, participants, and the study team members who participated 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.

Target Population and Sample Size

Participants were outpatient adults (≥ 18 years) with a documented positive severe acute respiratory syndrome coronavirus 2 (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.

Participants were randomized in a 1:1 ratio to receive a single 600 mg IM dose of AZD7442 or placebo. At least 60% of participants should have met the protocol definition of being at high-risk of progression to severe COVID-19. Based on the event-driven sample size calculation, enrollment was stopped 30 days after 43 events had been confirmed.

Participants at high-risk of progression to severe COVID-19 were 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 (body mass index > 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, human immunodeficiency virus, use of corticosteroids, or use of other immunosuppressive medicines
  - Sickle cell disease
  - Smoking (current or former)

The study had CCI to detect a relative risk reduction (RRR) of CCI in the incidence of severe COVID-19/death in the AZD7442 group compared to the placebo group, assuming the incidence of severe COVID-19/death in the placebo group was CCI.

Investigational Product and Comparator: Dosage, Mode of Administration and Batch Numbers

AZD7442 is a combination product of 2 monoclonal antibodies (mAbs), AZD8895 (tixagevimab) and AZD1061 (cilgavimab). A single dose comprises both mAb components administered in a fixed 1:1 ratio. Doses of AZD7442 are defined as the total mAb dose administered, eg, AZD7442 600 mg = AZD8895 300 mg + AZD1061 300 mg.

Each participant in this study received a single dose of either AZD7442 or placebo.

- AZD7442: 600 mg dose administered as 2 separate 300 mg 3 mL IM injections (one for AZD8895 and one for AZD1061) in the gluteal region.
- Placebo: participants randomized to placebo received saline placebo administered as 2 separate 3 mL IM injections in the gluteal region.

Batch numbers to be provided with final clinical study report (CSR).

Duration of Treatment

This is a single dose study. After administration of the IMP on Day 1, participants underwent 28 days of intensive follow-up, followed by an ongoing limited follow-up through Day 457. Therefore, the total study duration for each participant who completed the study is expected to be 457 days. Data in relation to the primary analysis and the Day 169 follow-up are included in this CSR, and the safety follow-up to Day 457 will be presented in a final CSR.

Statistical Methods

The primary efficacy endpoint was a composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 was characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (oxygen saturation [SpO_2] < 90% in room air and/or severe respiratory distress) and a World Health Organization Clinical Progression Scale score of 5 or higher.

The primary analysis was conducted 30 days after 43 primary endpoint events had been observed to allow follow-up for participants who may have been randomized at the time of the last event. A final analysis will be conducted when all participants have completed the study (ie, the final CSR will include data through the safety follow-up through Day 457).

The primary estimand was used for the analysis of the primary efficacy endpoint, based on participants in the modified full analysis set (mFAS) (all participants in the full analysis set [FAS] who received IMP ≤ 7 days from symptom onset and were not hospitalized at baseline (≤ Day 1) for isolation purposes).

For the primary efficacy analysis, the stratified Cochran-Mantel-Haenszel (CMH) method (by the stratification factors) was used. The relative risk was estimated by the CMH method, and the efficacy was calculated as the RRR = 100 × (1− risk ratio [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 confidence interval (CI) was presented. Participants who did not have an event and did not remain in the study until the Day 29 assessment, were 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 were generated for each randomized group. The Kaplan-Meier cumulative incidences were reported. A stratified Log-Rank test was conducted to assess the difference between the curves. A Cox-Proportional Hazards model was conducted to obtain hazard ratios and their respective 95% CIs. The stratification factors were included as covariates in the Cox model. Absence of data following participants' withdrawal/lost to follow-up were 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, was presented, along with the 2-sided 95% CI using the stratified Miettinen and Nurminen's score method.

The incidence of anti-drug antibody (ADA) to AZD7442 was assessed and summarized by number and percentage of participants who were ADA positive by treatment group. The ADA titer was listed by participant at different time points.

This report presents the results of the primary analysis and Day 169 key secondary endpoint for this study. The primary analysis was conducted 30 days after 43 primary endpoint events had been confirmed. Study data including the safety follow-up to Day 457 will be presented in a final CSR.

Study Population

The study is ongoing, and is being conducted at 95 sites across 14 countries (Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, United Kingdom, Ukraine, and United States of America).

At the time of the Key Secondary DCO, 910 participants had been randomized; 903 received the IMP. The demographic characteristics of the participants were generally balanced between treatment groups. Overall, 50.4% of participants were female and mean age was 46.1 years.

The study was enriched for high-risk participants with 89.8% of participants classified as high-risk.

Summary of Results

As TACKLE is an ongoing study, data continues to accumulate as participants complete protocol visits. The Day 29 efficacy analyses conducted at the Primary DCO (21 August 2021) up to Day 29 were repeated at the Day 169 Key Secondary DCO (14 January 2022) to confirm consistency with the Primary analysis.

For the primary analysis the median on-study follow-up time was 84.0 days. For the Key Secondary DCO the median on-study follow-up time was 170.0 days.

Efficacy

When the following analyses were repeated for the Key Secondary DCO the results were similar and did not change the interpretation of the endpoint. Unless otherwise indicated, in the synopsis, the Primary DCO is presented for the primary and secondary and exploratory endpoints, while for the key secondary, PK, ADA and safety endpoints the Key Secondary DCO is presented.

Primary: The primary endpoint was met. At the Primary DCO, treatment with AZD7442 compared with placebo led to a 50.49% (95% CI: 14.56 to 71.31; p-value 0.010) RRR for developing severe COVID-19 or death from any cause in non-hospitalized adults who had been symptomatic for 7 days or less. The study achieved statistical significance in the primary and all supportive estimands.

In participants who received treatment ≤ 5 days or ≤ 3 days from symptom onset, AZD7442 reduced the risk of developing severe COVID-19 or death versus placebo by 66.93% (95% CI: 31.11, 84.12) and 88.01% (95% CI: 9.40, 98.41), respectively.

Key Secondary: Treatment with AZD7442 compared with placebo led to a 49.11% (95% CI: 14.47, 69.72; p = 0.009) reduction in the composite endpoint of either death or hospitalization for COVID-19 complications or sequelae through Day 169.

Secondary: At the Primary DCO, treatment with AZD7442 compared with placebo reduced the incidence of respiratory failure by 71.86% (95% CI: 0.25, 92.06) through study Day 29.

For the majority of symptoms there was no difference between AZD7442 and placebo groups. At the Primary DCO, a reduction in symptom severity for the AZD7442 group compared to the placebo group was observed for cough and muscle aches; after the database had been updated at the Key Secondary DCO, these remained nominally significant. Symptom severity data were derived from self-reported e-diary data.

The number of participants with COVID-19 symptom progression through study Day 29 was 167 (54.9%) for AZD7442 versus 199 (62.2%) for placebo overall and regardless of baseline serology status: overall RRR 12.16 (95% CI: -0.20, 22.99); nominal p-value 0.053; serostatus positive at baseline RRR 16.88 (95% CI: -40.48, 50.82); nominal p-value 0.494; serostatus negative at baseline RRR 12.34 (95% CI: -0.38, 23.46); nominal p-value 0.056.

When assessing SARS-CoV-2 RNA in nasal swabs, treatment with AZD7442 resulted in a greater reduction in log10 SARS-CoV-2 RNA overall (Cohorts 1 and 2, analyzed at Day 6 and Day 29 only), at the Primary DCO, treatment with AZD7442 compared with placebo resulted in greater reductions in log10 SARS-CoV-2 RNA mean change from baseline at Day 6 (LS mean difference -0.39 [95% CI: -0.56 to -0.22]).

A separation of the return to usual health Kaplan-Meier curves favoring AZD7442 is apparent on visual inspection, however, there was no statistical difference (p-value 0.1499) in time to return to usual health by Day 29 in the AZD7442 group compared to the placebo group. The lack of statistical difference may reflect anchoring to Day 15 and Day 29 visits, which results in overlap of the curve at Day 29.

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Summary of Pharmacokinetic Results

After a single 600 mg IM dose of AZD7442, the mean serum concentrations of AZD8895 and AZD1061 over 168 days post-dose were similar. Serum drug concentration-time profiles over 168 days post-dose are consistent with the extended half-life of AZD7442.

Summary of Pharmacodynamic Results

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Summary of Immunogenicity Results

Over 168 days post-dose, ADA prevalence (% ADA positive to AZD8895 and/or AZD1061) and ADA incidence (% treatment-emergent [TE]-ADA positive [TE-ADA+] to AZD8895 and/or AZD1061) of AZD7442 in the active group were 25.7% (89/346) and 10.7% (37/346), respectively. The majority of ADA-positive participants were classified as non-TE-ADA+, indicating that ADA was either present prior to the initiation of treatment or baseline ADA titer did not meaningful increase (defined as ≤ 4-fold) following treatment.

The median of maximum ADA titers of AZD8895 and AZD1061 in TE-ADA+ participants in the AZD7442 group were 320.0 and 160.0, respectively, relative to the limit of detection of 80.0 and 40.0, respectively. These values were similar to those observed in TE-ADA+ participants in the placebo group at 320.0 and 320.0, respectively, indicating that the magnitude of ADA responses resulted from AZD7442 administration was no different than that which resulted from placebo administration. In addition, median ADA titer to AZD7442 (defined as the higher of the 2 titers of the individual mAbs) did not increase over 168 days post-dose (range 40 to 80, relative to the limit of detection of 40), suggesting that maturation of AZD7442 ADA did not occur over time.

The presence of ADA had no clear clinically relevant effect on AZD7442 PK. Available data show no clear evidence of an association of ADA with impact on efficacy or safety of AZD7442. The overall results demonstrate that AZD7442 has a low immunogenicity risk.

Summary of Pharmacokinetic/Pharmacodynamic Relationships: Not Applicable

Summary of Safety Results

Adverse events: At the time of the Primary DCO, 132 (29.2%) participants on AZD7442 and 163 (36.1%) participants on placebo had experienced at least one adverse event (AE) on study, and at the time of the Key Secondary DCO (median follow-up of 170 days) the rates increased in both groups to 174 (38.5%) and 196 (43.5%) participants, respectively.

At the Key Secondary DCO (median follow-up 170 days), the number of participants with related AEs or serious adverse events (SAEs), AEs leading to study withdrawal, and adverse events of special interest (AESIs) was unchanged since the Primary DCO (median follow-up 84 days). The number of participants with AEs, SAEs, AEs with outcome of death, AEs leading to study withdrawal, Grade 3 or 4 AEs, and AESIs were either lower in the AZD7442 group or similar between the AZD7442 and placebo groups. The number of related AEs (relatedness to IMP, as determined by the investigator) were balanced between groups and there were no related SAEs reported. No deaths were considered related by the Investigator.

No Grade 3 or 4 AE was judged by the Investigator to be possibly related to IMP. There were no Grade 3 or 4 AESIs.

Deaths: At the time of the Key Secondary DCO, 7 (1.5%) participants in the AZD7442 group and 6 (1.3%) participants in the placebo group had an AE with an outcome of death; one death (colorectal cancer metastatic PPD) in the AZD7442 group was reported between the Primary and Key Secondary DCOs. Within the SOC Infections and infestations, there were fewer deaths in the AZD7442 group (3 [0.7%]) compared with the placebo group (6 [1.3%]); this was due to fewer deaths with a preferred term including COVID19. No deaths were considered related to the IMP by the Investigator.

Serious adverse events: At the time of Key Secondary DCO, the number of participants with SAEs was lower in the AZD7442 group (40 [8.8%]) compared with the placebo group (61 [13.5%]). No SAEs were assessed as possibly related to IMP by the Investigator. The most commonly reported SOCs were Infections and infestations (75 [8.3%]), Nervous system disorders (5 [0.6%]), Cardiac disorders (5 [0.6%]), Hepatobiliary disorders (4 [0.4%]), and Injury, poisoning, and procedural complications (4 [0.4%]).

The number of participants with SAEs was generally balanced between groups within SOC and PT. However, within the SOC Infections and infestations, the numbers of participants with SAEs were lower in the AZD7442 group (27 [6.0%]) compared to the placebo group (48 [10.6%]). This was primarily driven by the preferred terms of COVID-19 and COVID-19 pneumonia, both of which were higher in placebo compared to AZD7442.

At the time of Key Secondary DCO, no new Cardiac SAEs in the AZD7442 group had been reported, 2 were reported for placebo. The number of participants with Cardiac disorders SOC SAEs was 2 (0.4%) in the AZD7442 group and 3 (0.7%) in the placebo group. All cardiac related SAEs occurred in participants with elevated cardiovascular risk (eg, age > 65 years, cardiac history, and hypertension) and were confounded by medical history. None of the Cardiac disorders SAEs were assessed as possibly related to IMP by the Investigator. No new thromboembolic SAEs occurred between the Primary and Key Secondary DCOs. Overall, thromboembolic SAEs were reported in 4 participants; 2 in the placebo group (portal vein thrombosis and superior sagittal sinus thrombosis) and 2 in the AZD7442 group (pulmonary embolism and peripheral artery thrombosis); all events were reported prior to the Primary DCO. None of these SAEs were assessed as possibly related to IMP by the Investigator.

Adverse events leading to discontinuation: No new AEs leading to discontinuation occurred between the Primary and Key Secondary DCOs. Overall, the number of participants discontinuing the study due to AEs was low 5 (1.1%) in the AZD7442 group and 7 (1.6%) in the placebo group. The majority of discontinuations were due to participant death. No participants in the AZD7442 group and 2 (0.4%) participants in the placebo group discontinued due to non-fatal AEs (PTs: COVID19 pneumonia, asthenia).

Adverse events of special interest: No new AESIs occurred between the Primary and Key Secondary DCOs. The protocol-defined AESIs for AZD7442 were anaphylaxis and other serious hypersensitivity reactions (including immune complex disease), and injection site reactions. At the Key Secondary DCO, the number of participants with AESIs was 15 (3.3%) in both groups. No anaphylaxis or other serious hypersensitivity reactions have been reported. The majority (27 [3.0%]) of AESIs were injection site reactions. Only 3 AESIs of Skin and subcutaneous tissue disorders were reported; none of them were serious. Overall, AESIs were balanced between the AZD7442 and placebo groups.

All the AESIs were assessed as possibly related to IMP by the Investigator (AZD7442 15 [3.3%]; placebo 15 [3.3%]). None were Grade 3 or 4 in severity or SAEs.

Vital signs: There were no notable differences in vital signs, electrocardiograms, physical findings, or other observations related to safety.

Clinical laboratory assessments: There were no notable differences between the treatment groups in clinical chemistry, clinical hematology, coagulation, or urinalysis.

Conclusion(s)

- The primary analysis showed that AZD7442 administered as a treatment for mild to moderate COVID-19 reduced the risk of developing severe COVID-19 or death from any cause by 50.49% (95% CI: 14.56, 71.31; p-value 0.010) compared to placebo. This was achieved in a setting where the majority of participants were at high-risk of severe disease.
- Participants treated early in their disease course derive the most benefit; in participants who received treatment ≤ 5 days or ≤ 3 days from symptom onset, AZD7442 reduced the risk of developing severe COVID-19 or death versus placebo by 66.93% (95% CI: 31.11, 84.12) and 88.01% (95% CI: 9.40, 98.41), respectively.
- After the primary analyses were repeated at the Key Secondary DCO there was no change to the efficacy conclusions.
- The findings of the key secondary endpoint aligned with the primary endpoint; showing that treatment with AZD7442 compared with placebo led to a 49.11% (95% CI: 14.47, 69.72; p = 0.009) RRR for the composite endpoint of either death or hospitalization for COVID-19 complications or sequelae through Day 169. CCI [redacted]
- With a median follow-up of 170 days, the results demonstrated an acceptable safety profile with no new safety findings observed for AZD7442 in this study.
- Between the Primary DCO and the Key Secondary DCO there were no new AEs leading to study withdrawal, any AESIs, or related AEs. No new Cardiac Events occurred in the AZD7442 group and no new thromboembolic events in either treatment group.

- After a single 600 mg IM dose of AZD7442, the mean serum concentrations of AZD8895 and AZD1061 over 168 days post-dose were similar. Serum concentration-time profiles over 168 days post-dose are consistent with the extended half-life of AZD7442.
- CCI [redacted]
- Incidence of TE-ADA to AZD7442 was (10.7%). The majority of ADA-positive participants were classified as non-TE-ADA+. The magnitude of ADA responses resulted from AZD7442 administration was no different than that which resulted from placebo administration. The presence of ADA had no clinically relevant effect on AZD7442 PK, and available data show no evidence of an association of ADA with impact on efficacy or safety of AZD7442.
- AZD7442 600 mg IM has a positive benefit-risk profile for the treatment of mild to moderate COVID-19.