Clinical Study Report	
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A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19

Study dates:	First participant randomized: 28 August 2020 Last participant randomized: 25 January 2021 The analyses presented in this report are based on a clinical data cut-off date of 05 March 2021
Phase of development:	Therapeutic confirmatory (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

Study Centers

Participants were enrolled at 88 study centers in 3 countries (United States of America [USA], Chile, and Peru).

Publications

At the time of writing this report, the following publication has been published:

Falsey 2021a

Falsey AR, Sobieszczyk M, Hirsch I, Sproule S, Robb M, Corey L et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 Vaccine. N Engl J Med. 2021 Sep 29. doi: 10.1056/NEJMoa2105290.

Objectives and Criteria for Evaluation

This Clinical Study Report (CSR) reports the primary analysis for AZD1222 compared with placebo, which occurred at a data cut-off date of 05 March 2021. An addendum to this CSR will be provided following the 6-month median follow up analysis, and a final analysis will be reported at a later date. The study objectives and endpoints described in this section are per the Clinical Study Protocol (CSP) Amendment 7.

The study objectives and criteria for evaluation are presented in Table S1, Table S2, and Table S3.

Table S1 Primary Objectives and Endpoints

Primary objectives	Estimand description [a]/Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19	Population: Fully vaccinated analysis set
	Endpoint: A binary response, whereby a participant with negative serostatus at baseline is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.
	Intercurrent events: For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawals will be treated as missing (ie, counted as not having met the criteria); participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from primary endpoint analysis. Participants unblinded to treatment assignment prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding.
	Summary measure: VE, calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)
• To assess the safety and tolerability of 2 IM doses of AZD1222 compared to saline placebo	• Incidence of AEs for 28 days post each dose of study intervention • Incidences of SAEs, MAAEs, and AESIs from Day 1 post treatment through Day 730
• To assess the reactogenicity of 2 IM doses of AZD1222 compared to saline placebo (Substudy only) [b]	• Incidences of local and systemic solicited AEs for 7 days post each dose of study intervention

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable

[b] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.
Illness Visits: Participants who presented with qualifying symptoms were tested for SARS CoV-2 and, if positive, completed Illness Visits.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; IM = intramuscular; MAAE = medically attended adverse event; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America; VE = vaccine efficacy.

Table S2 Secondary Objectives and Endpoints

Secondary objectives	Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of SARS-CoV-2 infection	• The incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention [a]
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of symptomatic COVID-19 using CDC criteria	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using CDC criteria
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of University of Oxford-defined symptomatic COVID 19	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, regardless of evidence of prior SARS-CoV-2 infection [a]
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of severe or critical symptomatic COVID-19	• The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention [a] • The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post first dose of study intervention
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related emergency department visits	• The incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose of study intervention [a]

Secondary objectives	Endpoints
• To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [b, c]	• Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies (MSD serology assay) • The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay)
• To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [b, c]	• Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay) • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay)
• To estimate the efficacy of AZD1222 compared to saline placebo for the prevention of COVID-19 following the first dose	• The incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention

[a] Key secondary endpoint.

[b] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.

[c] Illness Visits: Participants who presented with qualifying symptoms were tested for SARS CoV-2 and, if positive, completed Illness Visits.

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; MSD = Meso Scale Discovery; RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; S = Spike; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America.

The exploratory objectives to assess the long-term safety and tolerability of 2 intramuscular (IM) doses of AZD1222, and the durability of efficacy of 2 IM doses of AZD1222 against symptomatic coronavirus disease-2019 (COVID-19) and against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, were not planned for the primary analysis; these are planned for the 6-month median follow up analysis. Some of the exploratory objectives were not evaluated as of the data cut-off date of 05 March 2021 because, at the time of data cut-off, results were not yet available and were not included in the assessment of efficacy and immunogenicity summarized in this report. These objectives are greyed out in Table S3 below, for ease of reference.

Table S3 Exploratory Objectives and Endpoints

Exploratory objectives	Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the all-cause mortality	• The incidence of all-cause mortality from Day 1 through Day 730
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for COVID-19-related deaths	• The incidence of COVID-19-related deaths occurring from Day 1 through Day 730
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related hospitalizations	• The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention • The incidence of COVID-19-related hospitalizations occurring post first dose of study intervention
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related ICU admissions	• The incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention • The incidence of COVID-19-related ICU admissions occurring post first dose of study intervention
• To quantify SARS-CoV-2 viral loads in infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [a, b]	• Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR
• To characterize sequence variations in SARS-CoV-2 through genotypic analyses in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Genotypic analysis of SARS-CoV-2 from NP swabs collected on Day 1 Illness Visit [c]
• To quantify duration of viral shedding in symptomatic SARS-CoV-2 infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Duration of SARS-CoV-2 shedding in saliva over time
• To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Biophysical parameters, including, but not limited to, to serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from Illness Visits Day 1 through Day 28
• To assess symptoms associated with COVID-19 using an e-diary in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Symptoms recorded by participants in an Illness e-diary from Illness Visits Day 2 through Day 28

Exploratory objectives	Endpoints
• To assess SARS-CoV-2 specific antibodies in an ACE2 competition assay following 2 IM doses of AZD1222 or saline placebo (Illness Visits and Substudy only) [b, d]	• Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ACE2 competing antibodies from serum samples • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) in ACE2 competing antibodies
• To assess B- and T-cell responses following 2 IM doses of AZD1222 or saline placebo (Illness Visits and Substudy only) [b, d]	• Quantification of (IFN-γ) ELISpot responses to SARS CoV-2 S protein from day of dosing baseline to 14 days post each dose • Intracellular cytokine staining and flow cytometry for B- and T-cell responses from day of dosing baseline to 14 days post each dose
• To assess SARS-CoV-2 antibodies in nasal secretions following 2 IM doses of AZD1222 or saline placebo (Illness Visits and Substudy only) [b, d]	• Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in SARS-CoV-2 S, RBD, and Nucleocapsid antibodies (MSD serology assay) • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to SARS-CoV-2 S, RBD, and Nucleocapsid antigens (MSD serology assay)
• To assess anti-vector responses to the ChAdOx1 adenovirus vector following 2 IM doses of AZD1222 or saline placebo (Substudy only) [d]	• Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to AZD1222 as measured by ChAdOx1 neutralizing antibodies
• To assess additional immune responses following 2 IM doses of AZD1222 or saline placebo	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
• To assess the long-term safety and tolerability of 2 IM doses of AZD1222	• Incidences of SAEs, MAAEs, and AESIs post first dose of AZD1222 through Day 730
• To assess the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of AZD1222 through Day 360
• To assess the durability of efficacy of 2 IM doses of AZD1222 against SARS-CoV-2 infection	• The incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of AZD1222 through Day 730

Exploratory objectives	Endpoints

[a] Due to insufficient data for this objective at the initial 2-month data cut-off, these results will be reported at the 6-month median follow up analysis.

[b] Illness Visits: Participants who presented with qualifying symptoms were tested for SARS-CoV-2 and if positive, completed Illness Visits.

[c] Genotypic evaluations of SARS-CoV-2 were planned at the Day 1 and Day 14 Illness Visits. Supplemental genotypic evaluation may also have been performed at the Day 21 and Day 28 Illness Visits. Whole genome sequencing data collected from saliva samples were additionally assessed to provide supportive SARS-CoV-2 genotypic analyses.

[d] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.

Note: Some exploratory endpoints are shaded grey in the table because at the time of data cut-off date, results were not yet available and were being assessed and were not included in the assessment of efficacy and immunogenicity summarized in this report. The objectives to assess the long-term safety and tolerability of 2 IM doses of AZD1222, and the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19 and against SARS-CoV-2 infection were not planned for the primary analysis; these are planned for the 6-month median follow up analysis.

ACE2 = angiotensin-converting enzyme 2; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; ELISpot = enzyme-linked immunospot; GMFR = geometric mean fold rise; GMT = geometric mean titer; ICU = intensive care unit; IFN-γ = interferon-gamma; IM = intramuscular; MAAE = medically attended adverse event; MSD = Meso Scale Discovery; NP = nasopharyngeal; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction; RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; S = Spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America.

Study Design

Study D8110C00001 is an ongoing Phase III, randomized, double blind, placebo-controlled, multicenter study to assess the efficacy, safety, and immunogenicity of AZD1222 compared with saline placebo for the prevention of COVID-19. Open-label dosing was originally planned for Study D8110C00001 after an Emergency Use Authorization (EUA) was obtained in the USA. However, open-label dosing will not be implemented for this study, and the CSR and synopsis will not discuss open-label dosing.

Approximately 30000 participants were randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ viral particles [vp]) AZD1222 (n = approximately 20000) or saline placebo (n = approximately 10000) 4 weeks apart, on Days 1 and 29. Randomization was stratified by age (≥ 18 and < 65 years, and ≥ 65 years), with planned enrollment of at least 25% of participants in the older age stratum.

D8110C00001 was placed on clinical hold on 09 September 2020 due to an event of transverse myelitis reported in the University of Oxford-sponsored study COV002. The Food and Drug Administration (FDA) deemed it was safe to remove the clinical hold on 23 October 2020. The consequence of this hold is that approximately 800 study participants had a dosing interval > 4 weeks.

The first participants randomized in each age group in the USA, including 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222. These 3000 participants in the Substudy had additional assessments for pre-defined solicited AEs for 7 days post each dose of study intervention and for humoral and cellular immune responses. To further investigate cell-mediated immunogenicity, in particular, T helper cell type 1/T helper cell type 2 responses after AZD1222 or saline placebo administration, an immunogenicity cohort of approximately 300 participants was added.

The study design includes a 14-day Screening Period and a Treatment and Follow-up Period of up to 730 ± 30 days (including participants in the Substudy or immunogenicity cohort).

Participants who present with at least one of the qualifying symptoms listed in Section 4.1 of the CSP through Day 360 are assessed for COVID-19. With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more days. Participants with a COVID-19 qualifying symptom(s) are tested for SARS CoV-2, and, if positive, continue Illness Visit assessments.

Safety will be assessed for the duration of the study. Adverse events (AEs) were recorded for 28 days post each dose of study intervention (ie, until Day 29 post first dose and Day 57 post second dose), and serious adverse events (SAEs), medically attended AEs (MAAEs), and AEs of special interest (AESIs) will be recorded through Day 730.

A Protocol Safety Review Team (PSRT) provides support for blinded safety surveillance during the study. Additionally, an independent COVID-19 Vaccine Data and Safety Monitoring Board (DSMB) provides unblinded oversight to ensure safe and ethical conduct of the study. The COVID-19 Vaccine DSMB facilitated the interim analysis for efficacy and has the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and for making appropriate recommendations based on the available data. An independent blinded Neurological AESI Expert Committee is available to review and provide advice to the PSRT and the COVID-19 Vaccine DSMB on request about the diagnosis and causality assessment of selected neurological AESIs occurring in the AZD1222 clinical development program.

Target Population and Sample Size

The study population represented the initial target population for AZD1222 and included male and female adults ≥ 18 years of age who were not immunosuppressed but were at increased risk of SARS-CoV-2 infection due to their locations or circumstances. Inclusion of older adults was based on data that are being gathered from the ongoing University of Oxford-sponsored studies. The study excluded females who were pregnant or breastfeeding and individuals < 18 years of age.

Approximately 33000 participants were screened such that approximately 30000 participants were randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp) AZD1222 (the active group, n = approximately 20000) or saline placebo (the control group, n = approximately 10000) 4 weeks apart, on Day 1 and Day 29.

The sample size calculations are based on the primary efficacy endpoint and are derived following a modified Poisson regression approach. The calculations account for an interim and primary analysis, and the timing of these analyses are driven by the number of events observed in the study. A Lan-DeMets alpha-spending function is used to account for multiplicity across the interim and primary analysis, such that the overall Type I error was controlled at 5%. The calculations assumed minimal loss to follow up as it was anticipated that participants would remain engaged in the study. All participants are followed for the entire duration of the study.

For the primary efficacy analysis, approximately 150 events meeting the primary efficacy endpoint definition were required across the active and placebo groups within the population of participants who were seronegative at baseline to detect a vaccine efficacy (VE) point estimate of 60% with > 90% power. These calculations assumed an observed event rate of approximately 0.8% and were based on a 2-sided test, where the lower bound of the 2-sided 95.10% confidence interval (CI) for the VE point estimate was required to be greater than 30%, with an observed point estimate of at least 50%.

Investigational Product and Comparator: Dosage and Mode of Administration

Participants confirmed to be eligible were randomized 2:1 to either AZD1222 vaccine ($\geq 0.7 \times 10^{11}$ vp/mL unit dose strength and 5×10^{10} vp dosage level) or saline placebo, administered via 2 IM doses.

Duration of Treatment

This study consists of a Treatment and Follow-up period of up to 730 ± 30 days. Two doses were administered 4 weeks apart, on Days 1 and 29.

Statistical Methods

The primary efficacy endpoint and 4 key secondary endpoints were to be assessed at 2 time points during the study, giving an interim analysis and a primary analysis. The pre-planned interim analysis was included to support early assessment of efficacy prior to reaching the 150 events required for the primary analysis. The interim and primary analyses were in close proximity and, as such, the results from the primary analysis are the focus of this report.

A Lan-DeMets alpha spending function was used to account for multiplicity of the primary endpoint across the 2 time points. Given that statistical significance was achieved at the

interim analysis, the primary analysis presented estimates with nominal 2-sided 95% CI, and statistical significance was achieved if the 2-sided CI was > 30%. At the primary analysis, the success criterion for the study was nominally statistically significant, with an observed VE point estimate of at least 50%. If the primary endpoint achieved statistical significance at the 5% level at the primary analysis, a hierarchical approach was used to control for multiplicity of the primary and key secondary efficacy endpoints. That is, the null hypotheses for these efficacy endpoints were tested in a hierarchical order, and the subsequent null hypothesis was tested at a nominal significance level of 5% (2-sided) at the primary analysis, only if the prior null hypothesis was rejected.

A formal assessment of the key secondary efficacy endpoints at the primary analysis was only conducted if the statistical significance of the primary efficacy endpoint was demonstrated at nominal 2-sided alpha of 5% at the primary analysis. Therefore, no further multiplicity adjustment was necessary.

This study is conducted by multiple investigators at multiple centers internationally. Data from all centers are pooled together in the analyses, and there are no plans to perform an analysis of homogeneity of the results across centers.

Primary Efficacy Endpoint

The COVID-19-related endpoints, including the primary endpoint, are based on case adjudication.

The primary efficacy analysis of the primary endpoint was performed on the fully vaccinated analysis set (FVS). For participants who withdrew from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawals (or lost to follow up, death not caused by SARS-CoV-2) was treated as missing. Participant follow up time was censored at the time of unblinding or EUA COVID-19 vaccine administration, whichever occurred first. A Poisson regression model with robust variance adjusting for follow up time was used as the primary efficacy analysis model to estimate the relative risk (RR) on the incidence of SARS CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR)-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention between the AZD1222 and the placebo groups. The model contained the terms of study arm and age group at the time of informed consent (ie, ≥ 18 to < 65 years, and ≥ 65 years) as covariates.

Vaccine efficacy, which was the incidence in the vaccine group relative to the incidence in the control group expressed as a percentage, was calculated as a relative risk reduction (RRR) = 1- RR. Relative risk reduction and its corresponding 2-sided 95% CI was estimated from the Poisson regression model with robust variance. In addition, the 2-sided p-value testing null hypothesis that the VE was equal to 30% was obtained from the model. Statistical significance was achieved if the 95% CI for VE was > 30%. The success criterion

for the study is nominal statistical significance with an observed VE point estimate of at least 50%.

As a sensitivity analysis to the handling of missing data in the analysis of the primary efficacy endpoint, the primary analysis of the primary efficacy endpoint was repeated with multiple imputation for intercurrent events, without using log follow-up time as offset.

To support the primary analysis, a Cox Proportional Hazards (PH) model using the same covariates as for the primary analyses as well as Kaplan-Meier curves was presented for the active and control groups based on observed events, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention. The primary analysis was repeated on the per-protocol analysis set (PPS) as a supplementary analysis. Same 2-sided p-value testing null hypothesis that the VE is equal to 30% was presented. Additionally, the primary analysis was repeated, excluding participants with out-of-window vaccination due to the clinical hold, and without censoring at study unblinding or authorized COVID-19 vaccine administration.

For subgroup analyses, the FVS was used, except for the subgroup analysis for serostatus at baseline, which used the FVS regardless of baseline serostatus. Treatment by subgroup interaction was tested using the Poisson regression with robust variance model adjusting for follow-up time with the terms of treatment, age group, subgroup, and treatment-by-subgroup interaction.

Safety Objectives

All safety summaries were presented by study arm based on the safety analysis set (SAF). There were no statistical comparisons between the study arms for safety data.

Study Population

As of the cut-off date of 05 March 2021, 32379 participants had been randomized and received at least one dose of study intervention (21583 received AZD1222 and 10796 received placebo) (ie, included in the all participants analysis set). A total of 30720 participants (94.7%) had received 2 doses of study intervention, with 20769 participants receiving AZD1222. Nearly all (96.7%) participants were ongoing in the study at the time of data cut-off date (21090 [97.5%] participants in the AZD1222 group and 10305 [95.3%] in the placebo group). The percentage of participants who had discontinued from the study was 3.3%, and the most common reasons were withdrawal by participant (362 participants [66.4% of those who discontinued] in the AZD1222 group, 408 [79.8% of those who discontinued] in the placebo group) and lost to follow up (157 participants [28.8% of those who discontinued] in the AZD1222 group, 86 [16.8% of those who discontinued] in the placebo group).

The demographic characteristics in the FVS were generally similar among participants who received AZD1222 and placebo. The mean age of participants was 49.9 years and the majority

(79.0%) of the participants were aged 18 to 64 years, with 21.0% of participants aged ≥ 65 years. Overall, 56.3% were male, 79.2% were White, 23.3% were Hispanic or Latino, 87.3% were in the USA, and the mean body mass index (BMI) was 28.7 kg/m^2. At least one protocol-defined high-risk condition for severe COVID-19 was present in 59.1% of participants. For the SAF, 95.4% and 2.8% of total participants were seronegative or seropositive, respectively, at baseline, with similar proportions between study intervention groups.

The characteristics of pre-defined comorbidities based on presence or absence of Centers for Disease Control and Prevention (CDC) risk factors for severe COVID-19 disease were generally similar among participants who received AZD1222 and placebo. The presence of these pre-defined risk factors was assessed at screening. Overall, 59.1% of participants had at least one comorbidity, and the proportion of participants with comorbidities in each treatment arm was similar. The most common comorbidities were obesity, high blood pressure, a history of smoking, and asthma.

The median dosing interval was 29.0 days for both study intervention groups using the overall SAF and when limited to those participants who were randomized after removal of the clinical hold. Of note, a small percentage of participants (< 2.5%) received study intervention outside of the dosing interval; the maximum dosing interval due to the clinical hold was 148 days (approximately 21 weeks) for the AZD1222 group and 154 days (22 weeks) for the placebo group. Using the FVS, the median dosing interval was 29.0 days for both study intervention groups, and the majority of participants in the AZD1222 and placebo groups received their second dose within the CSP allowable window of ≥ 26 days to ≤ 36 days (95.7% and 95.3% of participants, respectively).

Summary of Efficacy Results

Duration of follow up

As of the data cut-off date of 05 March 2021, regardless of unblinding events, the median durations of follow up in the FAS from the second dose in both the AZD1222 group and placebo group were approximately 60 days; and the median duration of follow up from first dose was approximately 90 days.

Primary efficacy endpoint

In the primary efficacy analysis using 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 RT-PCR-positive symptomatic illness, with a lower bound of the 95.0% CI of 65.34% and a 2-sided nominal p-value of < 0.001 for testing H0: VE = 30%, which met the pre-specified success criterion.

Using the FVS, the primary endpoint result was robust to different imputation approaches for missing data and still met the pre-specified success criterion, including imputation using the higher placebo event rate.

A series of supplementary analyses were also conducted as pre-specified in the Statistical Analysis Plan. All analyses demonstrated VE estimates that were consistent with the primary efficacy analysis (point estimates approximately 74.0%) and included time to first event and changes to which participants were included in the analysis (ie, analysis set, participants whose timing of the second dose was impacted by clinical hold, and contribution of different data that were considered during adjudication).

Vaccine efficacy estimates across subgroups based on age, gender, ethnicity, BMI, and presence of pre-defined comorbidities were consistent with the VE estimate for the overall population.

Secondary efficacy endpoints

All of the 4 key secondary endpoints were statistically significant using the hierarchical fixed sequence testing method and were analyzed for events ≥ 15 days post second dose:

- First case of SARS-CoV-2 RT-PCR positive symptomatic illness regardless of evidence of prior SARS-CoV-2 infection (VE estimate [95% CI] of 73.7% [65.13, 80.13]).
- Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness (VE estimate [95% CI] of 100.0% [71.62, NE] due to no cases in the AZD1222 group).
- Incidence of COVID-19-related emergency department visits (VE estimate [95% CI] of 94.8% [58.98, 99.34]).
- Incidence of the first post-treatment response for SARS-CoV-2 Nucleocapsid antibodies regardless of symptoms (VE estimate [95% CI] of 64.3% [56.05, 71.03]).
  (Note: confirmatory change to positive PCR was not required, only seroconversion.)

Evaluation of efficacy using the CDC or University of Oxford-defined criteria resulted in consistent conclusions relative to the primary efficacy analysis (VE estimates [95% CI] of 69.7% [60.68, 76.57] and 70.7% [61.62, 77.64], respectively).

Efficacy following first dose demonstrated a VE estimate (95% CI) of 54.5% (46.48, 61.26) against symptomatic illness and a VE estimate (95% CI) of 85.0% (58.97, 94.50) against severe or critical illness.

Exploratory efficacy endpoints

At ≥ 15 days post second dose in the FVS and post first dose in the FAS, respectively, high VE estimates were demonstrated for hospitalizations (94.2% and 80.0%, which includes Intensive Care Unit (ICU) and non-ICU admissions) and ICU-admissions (100.0% and 75.7%).

A total of 88 of the 203 cases in the FVS had interpretable lineage data available, and the resulting VE estimate (95% CI) within this subgroup was consistent with the primary efficacy analysis (77.2% [64.48, 85.40]). A total of 101 of the 203 cases in the FVS had interpretable Spike next generation sequencing (NGS) data available, and the resulting VE estimate (95% CI) within this subgroup was also consistent with the primary efficacy analysis (74.9% [61.35, 83.66]). A small number of variants of concern or variants of interest were observed as of the data cut-off date (05 March 2021) by whole genome NGS of saliva samples and spike-specific NGS of nasopharyngeal (NP) swabs samples.

When the time to clearance of SARS-CoV-2 was assessed in the subset of participants receiving 2 doses of the investigational product (ie, in both the IAS and FVS) where the infection began at least 15 days post second dose, time to clearance of SARS-CoV-2 in saliva samples in AZD1222 vaccinated participants was notably shorter (11 vs 16 days) compared with participants in the placebo group.

Summary of Immunogenicity Results

Overall, AZD1222 generated a strong humoral response, including when stratified by age, race, and ethnicity.

Spike-binding and receptor binding domain-binding antibodies peaked at 14 days post second dose of AZD1222 (GMTs of 24224.11 AU/mL and 29487.39 AU/mL, respectively) and were maintained above the levels achieved by the first dose through at least Day (D)90.

Pseudoneutralizing antibody responses were elevated above baseline at 14 days post first dose of AZD1222 (geometric mean titer [GMT] = 41.37 AU/mL) with responses peaking at 28 days post second dose (GMT = 245.56 AU/mL).

Summary of Safety Results

Overall, vaccination with AZD1222 was well tolerated. As of the data cut-off date of 05 March 2021, 99.8% of participants (32379 out of 32451 randomized participants) were included in the SAF based on actual study intervention received; 21587 participants received AZD1222 and 10792 participants received placebo.

In the SAF, the proportion of participants at risk was balanced for all durations of follow up, with >90% of participants having had at least 60 days of follow up post first dose. Participants in the AZD1222 group in the SAF had a median duration of follow up post second dose of 61.0 days and participants had a median duration of follow up post first dose of 92.0 days, regardless of unblinding events; the duration of follow up was similar for the placebo group.

Solicited Adverse Events (Substudy)

Solicited AEs were local or systemic pre-defined events for assessment of reactogenicity. Solicited AEs were collected in a solicited AE e-diary only for participants in the Substudy and were assessed separately from the (unsolicited) AEs collected during the study. In the SAF, a total of 1956 participants in the AZD1222 group and 981 participants in the placebo group were evaluated for solicited AEs within 7 days after any dose. Within the first 7 days following any dose with AZD1222, solicited local and systemic AEs were reported by 74.1% and 71.6% of participants, respectively. In the placebo group, solicited local and systemic AEs were reported by 24.4% and 53.0% of participants, respectively. Most of the solicited local and systemic AEs following vaccination with AZD1222 were mild (Grade 1) or moderate (Grade 2) in severity. In the AZD1222 group, solicited local and systemic AEs were reported less frequently within 7 days post second dose (53.4% of participants and 47.3% of participants, respectively) than post first dose (68.3% of participants and 64.7% of participants, respectively).

Unsolicited Adverse Events

Unsolicited AEs were consistent with AEs commonly observed following vaccination. In the SAF, 40.6% of participants in the AZD1222 group and 29.7% of participants in the placebo group reported an unsolicited AE within 28 days after any dose. In the AZD1222 group, there were 26.6% of participants with an unsolicited AE within 28 days of the first dose and 24.4% of participants within 28 days of the second dose. The most frequently reported unsolicited AEs in the AZD1222 group were pain, headache, injection site pain, fatigue, and body temperature increased; all of which were reported at a higher frequency in the AZD1222 group compared with the placebo group. The majority of unsolicited events were mild to moderate in severity. Related unsolicited AEs, as determined by the investigator, were reported in 28.9% of participants in the AZD1222 group and 14.1% of participants in the placebo group following any dose. Related AEs were most commonly mild or moderate in severity.

Overall, 14 participants reported SAEs with a fatal outcome during the blinded study period, including 7 participants in the AZD1222 group (7 events reported) and 7 participants in the placebo group (9 events reported). None of the fatal events in either the AZD1222 or placebo groups were considered related to study intervention by the investigator. Overall, 7.5% of participants in the AZD1222 group and 7.6% of participants in the placebo group reported an MAAE. Overall, < 1% of participants reported an SAE (0.6% of participants in the AZD1222 group and 0.7% of participants in the placebo group). Only 1 participant in the AZD1222 group and 2 participants in the placebo group reported SAEs that were considered related to study intervention, as determined by the investigator. There were no clinically meaningful imbalances in the incidence of SAEs or MAAEs by system organ class (SOC) or preferred term (PT) between the AZD1222 and placebo groups. The incidence of study discontinuation

due to an AE was low; a total of < 0.1% of participants each in the AZD1222 and placebo groups discontinued the study due to AEs within 28 days following any dose.

The incidence of AESI was low (2.4% of participants in the AZD1222 group and 3.9% of participants in the placebo group). There were no clinically meaningful imbalances in the incidence of AESIs by AESI category or PT. In the "Neurologic" category, the proportions of participants who reported neurological AESIs were similar between the AZD1222 (0.5%) and placebo (0.4%) groups. In the "Potential Immune Mediated Conditions" (PIMC) category, the proportion of participants who reported PIMC AESIs was lower in the AZD1222 group (1.8%) compared with the placebo group (3.4%). In the "Vascular" category, few events were reported (0.1% in the AZD1222 group and < 0.1% in the placebo group); no imbalance was observed in this AESI category. In the "Hematologic" category, thrombocytopenia was reported in < 0.1% in the AZD1222 group, and immune thrombocytopenia was reported in < 0.1% in the placebo group. None of these participants reported a concurrent thromboembolic event.

Conclusions

- As of the data cut-off date of 05 March 2021, when administered as 2 IM doses of 5×10^{10} vp at an interval of approximately 4 weeks, the AZD1222 vaccine demonstrated a high degree of efficacy compared with saline placebo for the prevention of COVID-19 and SARS-CoV-2 infection.
  - In the primary efficacy analysis with 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 RT-PCR-positive symptomatic illness.
  - Vaccine efficacy estimates across subgroups based on age, gender, ethnicity, BMI, and presence of pre-defined comorbidities were consistent with the VE estimate for the overall population.
- Overall, AZD1222 generated a strong humoral response, including when stratified by age, race, and ethnicity.
- The AZD1222 vaccine had an acceptable safety profile and was well tolerated in healthy adult participants, as well as in high-risk adult populations of older adults and adults with comorbidities, who have an increased risk of death and severe disease associated with COVID-19.
  - Unsolicited AEs were consistent with AEs commonly observed following vaccination. The majority of solicited (local and systemic) AEs and unsolicited AEs following vaccination with AZD1222 were mild or moderate in severity and completely resolved within 2 to 3 days. Reactogenicity, as evaluated by the incidence of solicited AEs for 7 days post each dose, was lower following the second dose.
  - The incidences of SAEs and AESIs were low, and there were no clinically meaningful imbalances in the incidence of AESIs between the AZD1222 and placebo groups.

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4. LIST OF ABBREVIATIONS AND DEFINITONS OF TERMS

Abbreviation or special term	Explanation
ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse event of special interest
AZ	AstraZeneca
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease-2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	curriculum vitae
D	day
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FAS	full analysis set
FVS	fully vaccinated analysis set
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
H0	null hypothesis
IAS	immunogenicity analysis set
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
MAAE	medically attended adverse event
MLE	maximum likelihood estimate
MSD	Meso Scale Discovery

Abbreviation or special term	Explanation
NAESI	Neurological Adverse Event of Special Interest
NGS	next generation sequencing
NIAID	National Institute for Allergy and Infectious Diseases
NP	nasopharyngeal
MedDRA	Medical Dictionary for Regulatory Activities
PH	Proportional Hazards
PIMC	Potential Immune Mediated Conditions
PPS	per-protocol analysis set
PSRT	Protocol Safety Review Team
PT	preferred term
RBD	receptor binding domain
RR	relative risk
RRR	relative risk reduction
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome-associated coronavirus
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
SD	standard deviation
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
UK	United Kingdom
URC	Unblinded Review Committee
USA	United States of America
VE	vaccine efficacy
vp	viral particles
WHO	World Health Organization

5. ETHICS

5.1 Ethics Review

An IEC or IRB, as applicable for each study center, approved the final CSP, including the final version of the written/electronic ICF and any other information and/or materials to be provided to the study participants. The investigator ensured the distribution of these documents to the applicable IEC/IRB and to the study center staff. The opinion of the IRB was provided in writing. The investigator submitted the written approval to AstraZeneca (also referred to as 'AZ' or Sponsor) before enrollment of any participant into the study.

AstraZeneca (and/or its representatives) provides Regulatory Authorities, the IECs/IRBs, and the investigators with safety updates/reports according to local requirements, including SUSARs, where relevant.

The investigator is responsible for providing the IEC/IRB with reports of any SUSARs from any other study conducted with the study intervention. AstraZeneca provided this information to the investigator so that he/she could meet these reporting requirements.

Regulatory and ethical considerations for this study are summarized in the CSP (see Appendix A1 of the CSP [Appendix 16.1.1]). For a list of IRBs/IECs involved in this study, see Appendix 16.1.3.

5.2 Ethical Conduct of Study

This study is being performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

5.3 Study Participant Information and Consent

The investigator or his/her representative explained the nature of the study to the participant or his/her legally authorized representative and answered all questions regarding the study.

- Participants were informed that their participation was voluntary, and they were free to refuse to participate and could withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The study medical record included a statement that written/electronic informed consent was obtained before the participant was enrolled in the study and the date the written/electronic consent was obtained. The authorized person obtaining the informed consent also signed the ICF.

- Participants were re-consented to the most current version of the ICF(s) during their participation in the study if required by the IEC/IRB.
- A copy of the ICF(s) was provided to the participant or the participant's legally authorized representative.

Participants who were rescreened were required to sign a new ICF.

The ICF contained a separate section that addressed and documented the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee explained to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants were told that they were free to refuse to participate in any optional samples or the future use and could withdraw their consent in writing at any time and for any reason during the retention period. Participants who declined to participate in this optional research indicated this in the ICF. If a participant withdraws consent to the use of donated biological samples, the samples are disposed of/destroyed, and the action documented. If samples were already analyzed at the time of the request, AstraZeneca is not obliged to destroy the results of this research.

For a sample ICF, see Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Personnel at Study Centers

International co-ordinating investigators	Ann Falsey, MD University of Rochester School of Medicine 601 Elmwood Avenue, BOX 689 Rochester, NY USA 14642 Magda Sobieszczyk, MD Columbia University Irving Medical Center - Division of Infectious Diseases 180 Fort Washington Avenue, 6th and 9th floor New York, NY USA 10032
Investigators/clinical sites	The study is being conducted by 83 investigators at 88 study centers in 3 countries (USA, Chile, and Peru).

For a detailed list of personnel at the study centers, including copies of the CVs of the Principal Investigators, see Appendix 16.1.4.

6.2 AstraZeneca Study Personnel

For a detailed list of AstraZeneca personnel involved in the study, see Appendix 16.1.4.

6.3 Study Committees

6.3.1 Protocol Safety Review Team

A PSRT provided support for blinded safety surveillance during the study. For the PSRT charter and names of members, see Appendix 16.1.4.

6.3.2 Adjudication Charter

A blinded independent efficacy endpoint adjudication committee assesses symptomatic COVID-19 events and all deaths (see Section 9.7 for information on the adjudication process). Additional details are provided in the Efficacy Adjudication Committee Charter. For the detailed adjudication charter and names of adjudication charter members, see Appendix 16.1.4.

6.3.3 Data and Safety Monitoring Board

An independent COVID-19 Vaccine DSMB provided unblinded oversight to ensure safe and ethical conduct of the study. Full details of the COVID-19 Vaccine DSMB can be found in the COVID-19 Vaccine DSMB Charter. For the detailed DSMB charter and names of DSMB members, see Appendix 16.1.4.

6.3.4 Neurological Adverse Event of Special Interest Expert Committee

An independent blinded NAESI Expert Committee was available to review and provide advice to the PSRT and the COVID-19 Vaccine DSMB on request about the diagnosis and causality assessment of selected neurological AESIs. Full details of the NAESI Expert Committee can be found in the NAESI Expert Committee Charter. For the NAESI charter and names of the NAESI members, see Appendix 16.1.4.

6.4 Other Study Personnel

Table 1 presents details of other nonsponsor participants in this study.

Table 1 Other Nonsponsor Participants in the Study

Role in the study	Organization and address
Contract Research Organization	IQVIA Government Solutions Inc. 8280 Willow Oaks Corporate Drive, Suite 775 Fairfax, VA 22031, USA ClinChoice (Analysis and Reporting Services) 1300 Virginia Drive, Suite 408 Fort Washington, PA 19034, USA
Interactive Voice/Web Response System	Cenduit IRT 700 Park Offices Drive, Suite 250 Research Triangle Park, NC 27709, USA
Central laboratory services	Labcorp Drug Development (formerly Covance CLS) 1447 York Court Burlington, NC 27215-3361, USA LabCorp Drug Development (formerly Covance CLS) 8211 Scicor Drive Indianapolis, IN 46214, USA
Third party laboratory	PPD (Multiplex serology validation testing) 2244 Dabney Road Richmond, VA 23230-3323, USA Meso Scale Diagnostics (Immunogenicity in nasal secretions and serum ACE2 competition testing) 16020 Industrial Drive Gaithersburg, MD 20877, USA Vault Medical Services/Infinity Biologix LLC (Qualitative/Quantitative PCR testing for shedding; Whole genome sequencing of shedding specimens) 30 Knightsbridge Road Piscataway, NJ 08854, USA
Wearable device	Current Health, Inc 595 Pacific Ave., 4th Floor San Francisco, CA 94133, USA
eDiary and eConsent	IQVIA Study Hub 4820 Emperor Boulevard Durham, NC 27703, USA
DSMB support services (including interim analysis)	Everest Clinical Research Corporation 675 Cochrane Drive, East Tower, 4th Floor Markham, Ontario, Canada L3R 0B8
Medical writing	Impact Pharmaceutical Services Inc. 79 TW Alexander Drive, Suite 100 Research Triangle Park, NC 27709, USA

Role in the study	Organization and address
Thank you cards	Center for Information and Study on Clinical Research Participation One Liberty Square, Suite 1100 Boston, MA 02109, USA
Audit	Zigzag Associates Limited Innovation Centre, 99 Park Drive Abingdon Oxfordshire, OX14 4RY, UK

ACE2 = angiotensin-converting enzyme 2; COVID-19 = coronavirus disease-2019; ELISA = enzyme-linked immunosorbent assay; MSD = Meso Scale Diagnostics; PCR = polymerase chain reaction; qPCR = quantitative polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction; USA = United States of America.

For more details of other participants involved in the study, see Appendix 16.1.4.

6.5 Supplementary Information on Study Administrative Structure

For supplementary information on the study administrative structure, see Appendix 16.1.4.

7. INTRODUCTION

AZD1222 (also known as ChAdOx1 nCoV-19, COVID-19 Vaccine AstraZeneca, and Vaxzevria) is being developed for the prevention of COVID-19. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tPA leader sequence at the N terminus. Study D8110C00001 is an ongoing Phase III randomized, double-blind, placebo-controlled multicenter study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to saline placebo for the prevention of COVID-19. The purpose of this interim CSR is to provide available safety, efficacy, and immunogenicity data from the primary analysis (clinical data cut-off date of 05 Mar 2021) and the 2-month median follow up post second dose of study intervention, in adult study participants. An addendum to this CSR will be provided following the 6-month median follow up analysis, and a final analysis will be reported at a later date. A pre-planned interim analysis was included to support early assessment of efficacy prior to reaching the 150 events required for the primary analysis. The interim and primary analyses were in close proximity and, as such, the results from the primary analysis are the focus of this document. A final analysis will take place when all participants in the study have completed the study; study participants will be assessed for efficacy for one year, immunogenicity and safety for 2 years following the first dose of study intervention (Day 730).

The primary analysis was conducted, per CSP, from a data extraction performed on 19 March 2021, based on a data cut-off date of 05 March 2021. A total of 190 adjudicated events met the primary endpoint definition. This analysis was consistent with the pre-specified

plans according to the CSP and SAP. The high-level results from the primary analysis were shared with the DSMB and included in a corporate press release on 25 March 2021. Approximately 14 potential events meeting the primary endpoint criteria that occurred prior to the data cut-off date had not yet completed the adjudication process. Therefore, an updated data extraction was performed on 29 April 2021, based on the same data cut-off date of 05 March 2021, to ensure that all potential events had completed adjudication, pending laboratory results were available, and any data cleaning that occurred between 19 March 2021 and 29 April 2021 could be incorporated into an updated analysis. This report presents the results from the updated primary efficacy analysis.

7.1 Study Rationale

The aim of the study is to assess the safety, efficacy, and immunogenicity of AZD1222 for prevention of COVID-19. The COVID-19 pandemic has caused major disruption to healthcare systems as well as significant socioeconomic impacts. At the time of study initiation, there were no authorized or licensed preventions available against COVID-19, and accelerated vaccine development was urgently needed. A safe and effective vaccine for COVID-19 prevention will have a significant global public health impact.

7.2 Background

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and these patients were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV (Zhu et al 2020). The virus was subsequently renamed to SARS-CoV-2 because it is similar to the coronavirus responsible for SARS-CoV, a lineage B Betacoronavirus. Severe acute respiratory syndrome coronavirus 2 shares more than 79% of its sequence with SARS CoV, and 50% with the coronavirus responsible for MERS-CoV, a member of the lineage C Betacoronavirus (Randolph and Barreiro 2020). Coronavirus disease 2019 is the infectious disease caused by SARS-CoV-2. 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). By January 2020, there was increasing evidence of human-to-human transmission as the number of cases rapidly began to increase in China. Spread of the virus has been rapid and now encompasses the globe. The WHO declared the novel coronavirus a pandemic on 11 March 2020. Coronavirus disease in its most severe form can lead to acute respiratory distress syndrome with the acute onset of hypoxemia and bilateral pulmonary edema. Patients are at risk of developing severe systemic disease including coagulopathy, multi-systemic organ failure, and death. The WHO categorizes COVID-19 disease severity as mild, moderate, clinical deterioration, and critical illness. Global efforts to

contain the epidemic aim to avoid the most severe forms of disease that result in hospitalization and death, particularly among the most vulnerable adults with certain comorbidities or older age groups.

7.3 AZD1222

AZD1222 is a recombinant replication-deficient chimpanzee adenovirus encoding the SARS-CoV-2 S surface glycoprotein. AZD1222 is responsible for local expression of the S glycoprotein and is designed to stimulate/prime a protective immune response in the recipient towards the SARS-CoV-2 virus.

AZD1222 is assembled using the ChAdOx1 vector, which is derived from chimpanzee adenovirus Y25. The ChAdOx1 vector is replication-deficient, as the E1 gene region, essential for viral replication, has been deleted, rendering the vector unable to replicate in transduced cells. The E3 locus, which encodes immunomodulatory proteins that would suppress the immune response to a vaccine, is also deleted. The ChAdOx1 vector has been further modified to improve yields and hexon expression for immunotitration in complementing cell lines with the exchange of Y25 native E4 of 4,6, 6/7 genes for those in human adenovirus serotype 5. ChAdOx1 propagates only in cells expressing E1, such as HEK293 cells and derivative cell lines like T-REx-293.

7.4 Overview of the AZD1222 Clinical Development Program

Development of AZD1222, previously referred to as ChAdOx1 nCoV-19, was initiated by the University of Oxford, with subsequent development activities by AstraZeneca.

Study D8110C00001 is an ongoing double-blind, placebo-controlled, randomized study in approximately 30000 adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19. Participants received 2 doses of AZD1222 or saline placebo 4 weeks apart. The first participants randomized in each age group in the USA participated in a Substudy to assess immunogenicity and reactogenicity (3000 adults in total). Primary and secondary objectives evaluate the efficacy, safety, reactogenicity, and immunogenicity of AZD1222.
Note: D8110C00001 was placed on clinical hold on 09 September 2020 due to an event of transverse myelitis reported in the University of Oxford-sponsored study COV002. The FDA deemed it was safe to remove the clinical hold on 23 October 2020 because all clinical hold issues identified by the FDA were addressed. As a result of the hold, the Sponsor agreed to amend the CSP for Study D8110C00001, the associated ICF, as well as the AZD1222 IB, and also implemented enhanced safety monitoring procedures for the AZD1222 development program and, therefore, the clinical study subsequently continued. The consequence of this hold is that approximately 800 study participants had a dosing interval > 4 weeks.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary Objectives

This CSR reports the primary analysis for AZD1222 compared with placebo, which occurred at a data cut-off date of 05 March 2021. An addendum to this CSR will be provided following the 6-month median follow up analysis, and a final analysis will be reported at a later date. The study objectives and endpoints described in this section are per the CSP.

Table 2 Primary Objectives and Endpoints

Primary objectives	Estimand description [a]/Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19	Population: Fully vaccinated analysis set
	Endpoint: A binary response, whereby a participant with negative serostatus at baseline is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.
	Intercurrent events: For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawals will be treated as missing (ie, counted as not having met the criteria); participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from primary endpoint analysis. Participants unblinded to treatment assignment prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding.
	Summary measure: VE, calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)
• To assess the safety and tolerability of 2 IM doses of AZD1222 compared to saline placebo	• Incidence of AEs for 28 days post each dose of study intervention • Incidences of SAEs, MAAEs, and AESIs from Day 1 post treatment through Day 730
• To assess the reactogenicity of 2 IM doses of AZD1222 compared to saline placebo (Substudy only) [b]	• Incidences of local and systemic solicited AEs for 7 days post each dose of study intervention

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

[b] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.
Illness Visits: Participants who presented with qualifying symptoms were tested for SARS CoV-2 and, if positive, completed Illness Visits.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; IM = intramuscular; MAAE = medically attended adverse event; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America; VE = vaccine efficacy.

8.2 Secondary Objectives

Table 3 Secondary Objectives and Endpoints

Secondary objectives	Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of SARS-CoV-2 infection	• The incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention [a]
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of symptomatic COVID-19 using CDC criteria	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using CDC criteria
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of University of Oxford-defined symptomatic COVID 19	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, regardless of evidence of prior SARS-CoV-2 infection [a]
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of severe or critical symptomatic COVID-19	• The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention [a] • The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post first dose of study intervention

Secondary objectives	Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related emergency department visits	• The incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose of study intervention [a]
• To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [b, c]	• Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies (MSD serology assay) • The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay)
• To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [b, c]	• Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay) • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay)
• To estimate the efficacy of AZD1222 compared to saline placebo for the prevention of COVID-19 following the first dose	• The incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention

[a] Key secondary endpoint.

[b] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.

[c] Illness Visits: Participants who presented with qualifying symptoms were tested for SARS CoV-2 and, if positive, completed Illness Visits.

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; MSD = Meso Scale Discovery; RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; S = Spike; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America.

8.3 Exploratory Objectives

The objectives to assess the long-term safety and tolerability of 2 IM doses of AZD1222, and the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19 and against SARS-CoV-2 infection were not planned for the primary analysis; these are planned for the 6-month median follow up analysis. Some of the exploratory objectives were not evaluated as of the data cut-off date of 05 March 2021 because at the time of data cut-off,

results were not yet available and were not included in the assessment of efficacy and immunogenicity summarized in this report. These objectives are greyed out in Table 4, for ease of reference.

Table 4 Exploratory Objectives and Endpoints

Exploratory objectives	Endpoints
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the all-cause mortality	• The incidence of all-cause mortality from Day 1 through Day 730
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for COVID-19-related deaths	• The incidence of COVID-19-related deaths occurring from Day 1 through Day 730
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related hospitalizations	• The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention • The incidence of COVID-19-related hospitalizations occurring post first dose of study intervention
• To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related ICU admissions	• The incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention • The incidence of COVID-19-related ICU admissions occurring post first dose of study intervention
• To quantify SARS-CoV-2 viral loads in infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [a, b]	• Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR
• To characterize sequence variations in SARS-CoV-2 through genotypic analyses in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Genotypic analysis of SARS-CoV-2 from NP swabs collected on Day 1 Illness Visit [c]
• To quantify duration of viral shedding in symptomatic SARS-CoV-2 infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Duration of SARS-CoV-2 shedding in saliva over time
• To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Biophysical parameters, including, but not limited to, to serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from Illness Visits Day 1 through Day 28

Exploratory objectives	Endpoints
• To assess symptoms associated with COVID-19 using an e-diary in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	• Symptoms recorded by participants in an Illness e-diary from Illness Visits Day 2 through Day 28
• To assess SARS-CoV-2 specific antibodies in an ACE2 competition assay following 2 IM doses of AZD1222 or saline placebo (Illness Visits and Substudy only) [b, d]	• Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ACE2 competing antibodies from serum samples • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) in ACE2 competing antibodies
• To assess B- and T-cell responses following 2 IM doses of AZD1222 or saline placebo (Illness Visits and Substudy only) [b, d]	• Quantification of (IFN-γ) ELISpot responses to SARS CoV-2 S protein from day of dosing baseline to 14 days post each dose • Intracellular cytokine staining and flow cytometry for B- and T-cell responses from day of dosing baseline to 14 days post each dose
• To assess SARS-CoV-2 antibodies in nasal secretions following 2 IM doses of AZD1222 or saline placebo (Illness Visits and Substudy only) [b, d]	• Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in SARS-CoV-2 S, RBD, and Nucleocapsid antibodies (MSD serology assay) • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to SARS-CoV-2 S, RBD, and Nucleocapsid antigens (MSD serology assay)
• To assess anti-vector responses to the ChAdOx1 adenovirus vector following 2 IM doses of AZD1222 or saline placebo (Substudy only) [d]	• Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to AZD1222 as measured by ChAdOx1 neutralizing antibodies
• To assess additional immune responses following 2 IM doses of AZD1222 or saline placebo	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
• To assess the long-term safety and tolerability of 2 IM doses of AZD1222	• Incidences of SAEs, MAAEs, and AESIs post first dose of AZD1222 through Day 730
• To assess the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19	• The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of AZD1222 through Day 360

Exploratory objectives	Endpoints
• To assess the durability of efficacy of 2 IM doses of AZD1222 against SARS-CoV-2 infection	• The incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of AZD1222 through Day 730

[a] Due to insufficient data for this objective at the initial 2-month data cut-off, these results will be reported at the 6-month median follow up analysis.

[b] Illness Visits: Participants who presented with qualifying symptoms were tested for SARS-CoV-2 and, if positive, completed Illness Visits.

[c] Genotypic evaluations of SARS-CoV-2 were planned at the Day 1 and Day 14 Illness Visits. Supplemental genotypic evaluation may also have been performed at the Day 21 and Day 28 Illness Visits. Whole genome sequencing data collected from saliva samples were additionally assessed to provide supportive SARS-CoV-2 genotypic analyses.

[d] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.

Note: Some exploratory endpoints are shaded grey in the table because at the time of data cut-off date, results were not yet available and were being assessed and were not included in the assessment of efficacy and immunogenicity summarized in this report. The objectives to assess the long-term safety and tolerability of 2 IM doses of AZD1222, and the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19 and against SARS-CoV-2 infection were not planned for the primary analysis; these are planned for the 6-month median follow up analysis.

ACE2 = angiotensin-converting enzyme 2; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; ELISpot = enzyme-linked immunospot; GMFR = geometric mean fold rise; GMT = geometric mean titer; ICU = intensive care unit; IFN-γ = interferon-gamma; IM = intramuscular; MAAE = medically attended adverse event; MSD = Meso Scale Discovery; NP = nasopharyngeal; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction; RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; S = Spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America.

9. STUDY DESIGN AND PROCEDURES

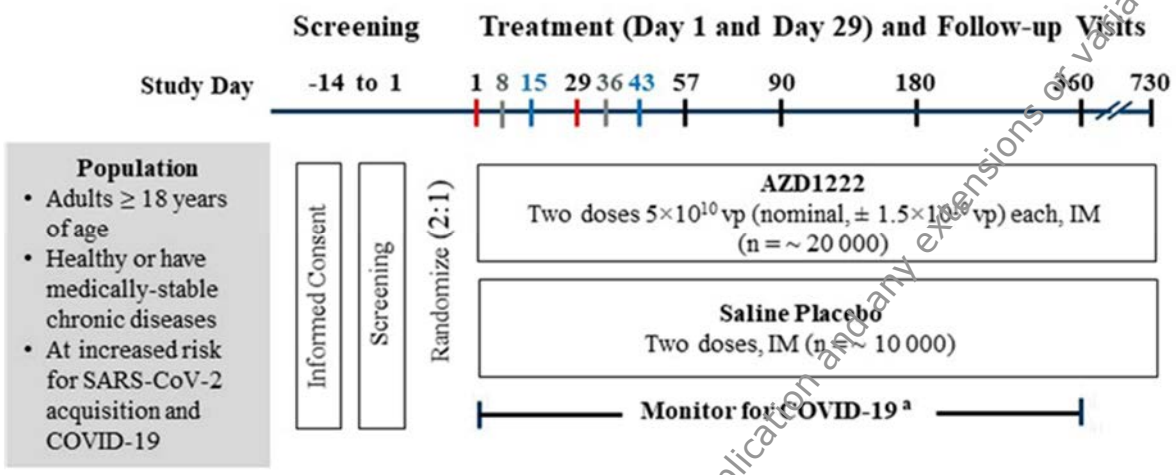
9.1 Overall Study Design

Study D8110C00001 is an ongoing Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and immunogenicity of AZD1222 compared with saline placebo for the prevention of COVID-19. Participants are adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19.

Open-label dosing was originally planned for Study D8110C00001 after an EUA was obtained in the USA. However, open-label dosing will not be implemented for this study, and this CSR will not discuss open-label dosing (details of open-label dosing can be found in the CSP Amendment 7 [Appendix 16.1.1]; for further details, see Section 9.9.1). A flow chart of

the overall study design is presented in Figure 1. The study design includes a 14day Screening Period and a Treatment and Follow-up Period of up to 730 ± 30 days.

Figure 1 Flow Chart of Study Design



[a] Participants who presented with qualifying symptoms were tested for SARS-CoV-2 and if positive, completed Illness Visits.

Red bars (Day 1 and Day 29): Administration of study intervention. Gray bars (Day 8 and Day 36): Visits were telephone contacts, not study site visits. Blue bars (Day 15 and Day 43): Visits were only for participants in the Substudy. The first participants randomized in each age group in the USA, including 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a substudy assessing the reactogenicity and immunogenicity of AZD1222. Black bars (Day 57, Day 90, Day 180, Day 360, and Day 730): Main study visits.

COVID-19 = coronavirus disease 2019; IM = intramuscular; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America; vp = viral particles.

Approximately 30000 participants were randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp) AZD1222 (n = approximately 20000) or saline placebo (n = approximately 10000) 4 weeks apart, on Days 1 and 29. Randomization was stratified by age (≥ 18 and < 65 years, and ≥ 65 years), with planned enrollment of at least 25% of participants in the older age stratum. Participants who received their first dose of study intervention between 28 August 2020 and 06 September 2020 received their second dose of study intervention outside of the study window (see Section 7.4).

The first participants randomized in each age group in the USA, including 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222. These 3000 participants in the Substudy had additional assessments for pre-defined solicited AEs for 7 days post each dose of study intervention and for humoral and cellular immune responses. For a definition of solicited AEs, see Section 8.3.7 of the CSP (Appendix 16.1.1).

Table 6 and Table 7 provide the SoA for the main study and Substudy, respectively.

To further investigate cell-mediated immunogenicity, in particular, T helper cell type 1/T helper cell type 2 responses after AZD1222 or saline placebo administration, an immunogenicity cohort of approximately 300 participants was planned. Participants followed the SoA in Table 7.

Participants who present with at least one of the qualifying symptoms listed in Section 4.1 of the CSP (Appendix 16.1.1) through Day 360 are assessed for COVID-19. With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more days. Participants with a COVID-19 qualifying symptom(s) are tested for SARS CoV-2, and, if positive, continue Illness Visit assessments, as presented in Table 8. See Section 8.1 of the CSP (Appendix 16.1.1) for details on COVID-19 assessments.

As the study is still ongoing, safety will be assessed for the duration of the study. Adverse events were recorded for 28 days post each dose of study intervention (ie, until Day 29 post first dose and Day 57 post second dose), and SAEs, MAAEs, and AESIs will be recorded through Day 730. See Sections 8.3, 8.3.8, and 8.3.9 of the CSP (Appendix 16.1.1), respectively, for definitions of these events.

A PSRT provides support for blinded safety surveillance during the study. Additionally, an independent COVID-19 Vaccine DSMB provides unblinded oversight to ensure safe and ethical conduct of the study. The COVID-19 Vaccine DSMB facilitated the interim analysis for efficacy and has the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and for making appropriate recommendations based on the available data. An independent blinded Neurological AESI Expert Committee is available to review and provide advice to the PSRT and the COVID-19 Vaccine DSMB on request about the diagnosis and causality assessment of selected neurological AESIs occurring in the AZD1222 clinical development program. See Appendix A 5 of the CSP (Appendix 16.1.1) for additional detail.

The SoA tables include:

- Table 5, Screening Period
- Table 6, Treatment and Follow-up Period – Main Study (Excluding Substudy and Immunogenicity Cohort Participants)
- Table 7, Treatment and Follow-up Period – Substudy and Immunogenicity Cohort (USA Participants Only)
- Table 8, Illness Visits (Participants with Qualifying Clinical Symptoms)

Table 5 Schedule of Activities: Screening Period

Procedure/Study day	Day -14 to Day 1 [a]	For details see CSP Section:
Informed consent: main study	X	5.1
Assignment SID number	X	6.3
Medical history	X	5.1, 5.2
Complete physical examination, including height and weight	X	8.2.1
Vital signs (including pulse oximetry)	X	8.2.2
Pregnancy test – urine or serum (WOCBP only) [b]	X	8.2.3
Assessment of SAEs	X	8.3
Concomitant medications	X	6.5
Verify eligibility criteria	X	5.1, 5.2

[a] If screening and dosing occurred at the same visit, only one evaluation was required.

[b] If urine tested positive or indeterminate, a quantitative serum β-hCG was performed for confirmation.

β-hCG = beta-human chorionic gonadotropin; CSP = Clinical Study Protocol; SAE = serious adverse event; SID = subject identification; WOCBP = women of childbearing potential.

Table 6 Schedule of Activities: Treatment and Follow-up Period – Main Study (Excluding Substudy and Immunogenicity Cohort Participants)

Procedure	**Treatment and Follow-up Period**									**For details see CSP Section:**
Day	**1**	**8 [a]**	**29**	**36 [a]**	**57**	**90**	**180**	**360**	**730**	
Window (days)	**NA**	**± 3**	**-3 to +7**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15**	**± 30**	
Medical history	X									5.1, 5.2
Targeted physical examination	X									8.2.1
Vital signs (including pulse oximetry)	X									8.2.2
Pregnancy test – urine or serum (WOCBP only) [b]	X (predose)		X (predose)							8.2.3
Concomitant medications	X	X	X	X	X	As applicable, for treatment of SAE, MAAE, or AESI [c]				6.5
Verify eligibility criteria	X									5.1, 5.2
Study intervention administration	X		X							6.1, 6.2
Efficacy assessments										
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms [d]	←							→		8.1.1
Nasal swab for SARS-CoV-2 RT-PCR (local laboratory)	X (predose)									
Serum sample for SARS-CoV-2 serology testing	X (predose)		X (predose)		X	X	X	X	X	8.5.2
Immunogenicity assessments										
Serum sample for exploratory assessment	X (predose)		X (predose)		X					8.5.2.5
Safety assessments										
AEs	X	X	X	X	X					8.3
SAEs, MAAEs, and AESIs	X	X	X	X	X	X	X	X	X	
Telephone contact for safety monitoring		X		X						

Procedure	Treatment and Follow-up Period									For details see CSP Section:
Day	1	8 [a]	29	36 [a]	57	90	180	360	730	
Window (days)	NA	± 3	-3 to +7	± 3	± 3	± 5	± 10	± 15	± 30	

[a] Not a study site visit; participants were contacted by telephone for safety monitoring.

[b] If urine tested positive or indeterminate, a quantitative serum β-HCG was performed for confirmation.

[c] Vaccinations, other than AZD1222, for prevention of SARS-CoV-2 or COVID-19 were recorded if administered at any time during the study.

[d] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they had qualifying symptoms.

AE = adverse event (treatment-emergent); AESI = adverse event of special interest; β-hCG = beta-human chorionic gonadotropin; COVID-19 = coronavirus disease 2019; CSP = Clinical Study Protocol; MAAE = medically attended adverse event; NA = not applicable; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; WOCBP = women of childbearing potential.

Table 7 Schedule of Activities: Treatment and Follow-up Period – Substudy and Immunogenicity Cohort (USA Participants Only)

Procedure	**Treatment and Follow-up Period**											**For details see CSP Section:**
Day	**1**	**8** [a]	**15**	**29**	**36** [a]	**43**	**57**	**90**	**180**	**360**	**730**	
Window (days)	**NA**	**± 3**	**± 1**	**-3 to +7**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15**	**± 30**	
Medical history	X											5.1, 5.2
Targeted physical examination	X											8.2.1
Vital signs (including pulse oximetry)	X											8.2.2
Pregnancy test – urine or serum (WOCBP only) [b]	X (predose)			X (predose)								8.2.3
Concomitant medications	X	X	X	X	X	X	X	As applicable, for treatment of SAE, MAAE, or AESI [c]				6.5
Verify eligibility criteria	X											5.1, 5.2
Study intervention administration	X			X [d]								6.1.1
Efficacy assessments												
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms [e]	←											8.1.1
Nasal swab for SARS-CoV-2 RT-PCR (local laboratory)	X (predose)											
Serum sample for SARS-CoV-2 serology testing	X (predose)		X	X (predose)		X	X	X	X	X	X	8.5.2
Immunogenicity assessments												
Serum sample for ChAdOx1 nAbs assessment	X (predose)			X (predose)			X		X	X	X	8.5.2
Serum sample for seasonal CoV serology testing	X (predose)			X (predose)			X		X	X		

Procedure	Treatment and Follow-up Period											For details see CSP Section:
Day	1	8 [a]	15	29	36 [a]	43	57	90	180	360	730	
Window (days)	NA	± 3	± 1	-3 to +7	± 3	± 3	± 3	± 5	± 10	± 15	± 30	
PBMCs for assessment of B-cell and T-cell responses [f]	X (predose)		X			X			X			8.5.2
Serum sample for SARS-CoV-2 nAb assessment	X (predose)		X	X (predose)		X	X		X	X		
Nasal adsorption for SARS-CoV-2 mucosal responses (optional)	X (predose)		X	X (predose)		X	X		X	X		
Serum sample for ACE2 competition serology	X (predose)			X (predose)			X		X			
Safety assessments												
Local and systemic pre-defined solicited AEs (recorded daily by participant in solicited AE e-diary) – substudy only	X (through Day 8)			X (through Day 36)								8.3.7
AEs	X	X	X	X	X	X	X					8.3
SAEs, MAAEs, and AESIs	X	X	X	X	X	X	X	X	X	X	X	
Telephone contact for safety monitoring		X			X							

[a] Not a study site visit; participants were contacted by telephone for safety monitoring.

[b] If urine tested positive or indeterminate, a quantitative serum β-hCG was performed for confirmation.

[c] Vaccinations, other than AZD1222, for prevention of SARS-CoV-2 or COVID-19 were recorded if administered at any time during the study.

[d] Participants who received their first dose of study intervention between 28 August 2020 and 06 September 2020 received their second dose of study intervention outside of the study window (see Section 7.4).

[e] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms.

[f] PBMCs were isolated from up to 300 participants in the Substudy and approximately 300 participants in the immunogenicity cohort at select study sites, as outlined in the laboratory manual.

ACE2 = angiotensin-converting enzyme 2; AE = adverse event (treatment-emergent); AESI = adverse event of special interest; β-hCG = beta-human chorionic gonadotropin; CoV = coronavirus; COVID-19 = coronavirus disease 2019; CSP = Clinical Study Protocol; FDA = Food and Drug Administration; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; PBMC = peripheral blood mononuclear cell;

Procedure	Treatment and Follow-up Period											For details see CSP Section:
Day	1	8 [a]	15	29	36 [a]	43	57	90	180	360	730	
Window (days)	NA	± 3	± 1	-3 to +7	± 3	± 3	± 3	± 5	± 10	± 15	± 30	

RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America; WOCBP = women of childbearing potential.

Table 8 Schedule of Activities: Illness Visits (Participants with Qualifying Clinical Symptoms)

Procedure [a]	Site visit	Home collection by participant				Site visit for SARS-CoV-2 positive participants only			For details see CSP Section:
Day	**1**	**3**	**5**	**8**	**11**	**14**	**21**	**28**	
Window (days)	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Medical history	X					X	X	X	8.1
Brief physical examination	X					X	X	X	8.2.1
Vital signs (including pulse oximetry)	X					X	X	X	8.2.2
Concomitant medication	←	—	—	—	—	—	—	→	6.5
Efficacy assessments									
Digital health device	←	—	—	—	—	—	—	→	8.1.2.2
Symptoms associated with COVID-19 (recorded daily by participant in Illness e-diary)	←	—	—	—	—	—	—	→	8.1.2.3
Virology assessments									
Nasal swab for SARS-CoV-2 RT-PCR (local laboratory)	X								8.1.2.1
Nasopharyngeal swab									
SARS-CoV-2 RT-PCR (central laboratory)	X					X	X	X	8.1.2.1
SARS-CoV-2 sequencing (central laboratory)	X					X			
Respiratory panel	X								8.6.1.1
Saliva sample for viral shedding [b]	X	X	X	X	X	X	X	X	8.6.1.2
Immunogenicity assessments									
PBMCs for B-cell and T-cell responses	X [c]					X			8.5.2
Serum sample for SARS-CoV-2 nAb assessment	X					X		X	
Nasal adsorption for SARS-CoV-2 mucosal responses (optional)	X					X		X	
Serum sample for ACE2 competition serology	X					X		X	8.5.2
Serum sample for exploratory assessments	X					X		X	

Procedure [a]	Site visit	Home collection by participant				Site visit for SARS-CoV-2 positive participants only			For details see CSP Section:
Day	**1**	**3**	**5**	**8**	**11**	**14**	**21**	**28**	
Window (days)	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Safety assessments									
SAEs, MAAEs, and AESIs	←	—	—	—	—	—	—	→	8.3
Telephone contact for safety monitoring		X		X					

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who tested positive continued with the Illness Visits, including any home collection requirements. Participants who tested negative for SARS-CoV-2 were instructed to stop all Illness Visit assessments and return the digital health device (see Section 8.1.2.2 of the CSP [Appendix 16.1.1]).

[b] Collection of saliva sample for viral shedding was optional in non-USA sites and was not conducted following completion of a feasibility assessment.

[c] PBMCs were collected from up to approximately the first 3000 participants, where operationally feasible, on Day 1 Illness Visit and any participants with a Day 1 SARS-CoV-2 positive test result by local RT-PCR test (see Section 8.3.2.4 of the CSP [Appendix 16.1.1]).

ACE2 = angiotensin-converting enzyme 2; AESI = adverse events of special interest; COVID-19 = coronavirus disease-2019; CSP = Clinical Study Protocol; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America.

9.2 Scientific Rationale for Study Design, Doses, and Control Groups

The rationale for the key features of the study design, choice of dose and dosing frequency, and choice of participant population is provided in greater detail in Sections 4.2 and 4.3 of the CSP (Appendix 16.1.1).

9.2.1 Rationale for Study Design and Participant Population

The participant population is comprised of male and female adults ≥ 18 years of age who were not immunosuppressed but were at increased risk of SARS-CoV-2 infection due to their locations or circumstances. Inclusion of older adults was based on data that are being gathered from the ongoing University of Oxford-sponsored studies. Study COV001 (NCT04324606) enrolled adults 18 to 55 years of age, Study COV002 (NCT04400838) enrolled adults ≥ 18 years of age, and Study COV006 (International Standard Registered Clinical/soCial sTudy Number 15638344) is currently evaluating AZD1222 in pediatric participants 6 to 17 years of age.

The study excluded females who were pregnant or breastfeeding and individuals < 18 years of age. Women who were pregnant or breastfeeding were excluded during enrollment, as nonclinical developmental and reproductive toxicity studies to support vaccinating these individuals were not completed prior to the end of enrollment.

The study population represented the initial target population for AZD1222. Given the favorable efficacy profile demonstrated by AZD1222 for the prevention of COVID-19, the safety and immunogenicity of the vaccine in additional groups such as the immunosuppressed and pregnant women may be assessed in future studies.

9.2.2 Rationale for Study Endpoints

This study, including the efficacy and safety endpoints, was designed to align with regulatory guidance on the development and licensure of COVID-19 vaccines (FDA 2020). The efficacy endpoints in this study are analogous to endpoints used for evaluating the efficacy of influenza vaccines. These definitions have 4 components: (1) a definition of clinical illness; (2) a method of respiratory specimen sampling for the detection of associated shedding of the relevant virus; (3) an assay method for laboratory confirmation; and (4) a defined surveillance period. Assessment of AZD1222 efficacy begins ≥ 15 days post second dose of study intervention, as this time period is considered necessary for the vaccine to induce protective immune responses.

In the Substudy, solicited AEs were collected for 7 days post each dose of study intervention, a period that had proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, unsolicited AEs were collected through 28 days post each dose of study intervention. Serious adverse events, MAAEs, and AESIs are collected from Day 1 through end of the study. Adverse events of special interest include terms identified by the

Brighton Collaboration involving events associated with vaccination in general (SPEAC 2020).

9.2.3 Justification for Dose

The AZD1222 dose of 5 x 10^{10} vp was selected based on accumulated clinical experience with this vaccine in ongoing clinical studies sponsored by the University of Oxford. Based on accumulating nonclinical and clinical data gathered for AZD1222 as well as for other SARS-CoV-2 vaccines in development, a 2-dose regimen was selected for the study in order to enhance the immune response to the virus. The 4-week interval was selected based on the interval used in nonclinical studies and Study COV001.

For further detail, see Section 4.3 of the CSP (Appendix 16.1.1).

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

For inclusion in the study, participants must have fulfilled all of the following criteria:

Age

1 Adult, ≥ 18 years of age at the time of consent

Type of Participant

2 Increased risk of SARS-CoV-2 infection
   - Defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment contemporaneous to enrollment (believed to be at risk/exposure)

3 Medically stable such that, according to the judgment of the investigator, hospitalization within the study period was not anticipated and the participant appeared likely to be able to remain on study through the end of protocol-specified follow up
   - A stable medical condition was defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months prior to enrollment

4 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

5 Contraceptive use by women should have been consistent with local regulations regarding the methods of contraception for those participating in clinical studies

6 Female participants:
   (a) Women of childbearing potential must:
   - Have had a negative pregnancy test on the day of screening and on Day 1

- Have used 1 highly effective form of birth control for at least 28 days prior to Day 1 and agreed to continue using one highly effective form of birth control through 60 days following administration of the second dose of study intervention. A highly effective method of contraception was defined as one that could achieve a failure rate of less than 1% per year when used consistently and correctly (see Table 7 of the CSP [Appendix 16.1.1]). Periodic abstinence, the rhythm method, and withdrawal were NOT acceptable methods of contraception.

(b) Women were considered of childbearing potential unless they met either of the following criteria:

- Surgically sterilized (including bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or
- Post-menopausal
- For women aged < 50 years, post-menopausal was defined as having both:
  - A history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment, and
  - A follicle-stimulating hormone level in the post-menopausal range
  - Until follicle-stimulating hormone was documented to be within menopausal range, the participant was to be considered of childbearing potential
- For women aged ≥ 50 years, post-menopausal was defined as having a history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment

Informed Consent

7 Capable of giving signed informed as described in Appendix A of the CSP (Appendix 16.1.1), which included compliance with the requirements and restrictions listed in the ICF and in the CSP.

9.3.2 Exclusion Criteria

Any of the following were regarded as a criterion for exclusion from the study:

Medical Conditions

1 History of allergy to any component of the vaccine
2 History of Guillain-Barré syndrome or any other demyelinating condition
3 Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the day prior to or day of randomization
4 History of laboratory-confirmed SARS-CoV-2 infection
5 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia
6 Recurrent severe infections and use of immunosuppressant medication within the past 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days

for ≥ 15 days within 30 days prior to administration of study intervention)
The following exceptions were permitted:

(a) Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

(b) Human immunodeficiency virus-positive stable participants on stable antiretroviral therapy (eg, NIH 2020, Waldrop et al 2016)

7 History of primary malignancy, except for:

(a) Malignancy with low potential risk for recurrence after curative treatment (for example, history of childhood leukemia) or metastasis (for example, indolent prostate cancer) in the opinion of the site investigator

(b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

(c) Adequately treated uterine cervical carcinoma in situ without evidence of disease

(d) Localized prostate cancer

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

9 Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the investigator (mild/moderate well-controlled comorbidities were allowed)

10 Any other significant disease, disorder, or finding that may have significantly increased the risk to the participant because of participation in the study, affected the ability of the participant to participate in the study, or impaired interpretation of the study data
Note: The AESIs outlined in Appendix E (including Table 15) of the CSP (Appendix 16.1.1) should have been considered when evaluating a participant for Exclusion Criterion 10, as the presence of these AESIs, especially if untreated or uncontrolled, may have been a safety risk to the participant, affected the ability of the participant to participate in the study, or impaired interpretation of the study data. Investigators should have reviewed and considered the list of conditions in Appendix F of the CSP (Appendix 16.1.1). If any of these conditions were present in a participant, the investigator was asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have had conditions as outlined in Appendix E of the CSP (Appendix 16.1.1) and the participant was enrolled, the investigator was asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

11 Receipt of, or planned receipt of, investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19
Note: For participants who became hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies was permitted

12 Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention

13 Receipt of immunoglobulins and/or any blood products within 3 months prior to administration of study intervention or expected receipt during the period of study follow up

Other Exclusions

14 Involvement in the planning and/or conduct of this study (applied to both Sponsor staff and/or staff at the study site)

15 For women only – was currently pregnant (confirmed with positive pregnancy test) or breast feeding

16 Had donated ≥ 450 mL of blood products within 30 days prior to randomization or expected to donate blood within 90 days of administration of the second dose of study intervention

9.3.3 Lifestyle Considerations

1 Participants must have followed the contraception requirements outlined in Section 9.3.1

2 Restrictions relating to concomitant medications described in Section 9.4.5

3 Agreed to wear digital health device if diagnosed with COVID-19, as described in Section 8.1.2.2. of the CSP (Appendix 16.1.1)

9.4 Study Treatments Administered

9.4.1 Identity of Investigational Products

The details of the study intervention are provided in Table 9 and in Section 6 of the CSP (Appendix 16.1.1).

For details on labeling, storage, and accountability of the study intervention, see Sections 6.1 and 6.2 of the CSP (Appendix 16.1.1). For details regarding site(s) of manufacture, see Appendix 16.1.4.

Table 9 Study Intervention

Intervention name	AZD1222	Placebo
Type	Vaccine	Placebo
Dose formulation	10 mM histidine, 7.5 % (w/v) sucrose, 35 nM sodium chloride, 1 mM magnesium chloride, 0.1% (w/v) polysorbate 80, 0.1 mM edetate disodium, 0.5% (w/v) ethanol, at pH 6.6	0.9% (w/v) saline
Unit dose strength(s)	$\geq 0.7 \times 10^{11}$ vp/mL	NA
Dosage level(s)	5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp)	NA
Route of administration	IM	IM
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Sourced locally
Packaging and labeling	Provided in vials within a carton. Each carton and vial were labeled as required per country requirement	NA
Current/former name or alias	ChAdOx1 nCoV-19	NA

IM = intramuscular; IMP = investigational medicinal product ; NA = not applicable; NIMP = non-investigational medicinal product; vp = viral particles; w/v = weight/volume.

All investigational products were to be kept in a secure place under appropriate storage conditions.

9.4.2 Medical Devices – Not Applicable

9.4.3 Measures to Minimize Bias: Randomization and Blinding

All participants were centrally assigned to randomized study intervention using an IRT. Before the study was initiated, user guides, the log in information, and directions for the IRT were provided to each study site. Randomization was stratified by age (≥ 18 to < 65 years, and ≥ 65 years), with at least 25% of participants enrolled in the older age stratum. Additional details are provided in Section 6.3 of the CSP (Appendix 16.1.1).

For the responsible organization for generating the randomization scheme, see Appendix 16.1.4.

For the specific methods used to assign participants to treatment groups, see Section 6.3.1 of the CSP (Appendix 16.1.1). Neither the participants nor any of the investigators or Sponsor staff who were involved in the treatment or clinical evaluation and monitoring of the participants were aware of the study intervention received unless they were unblinded for safety reasons or receipt of an EUA vaccine other than AZD1222. Since AZD1222 and saline placebo were visually distinct prior to dose preparation (due to differences in container

closure), study intervention was handled by an unblinded pharmacist (or designee in accordance with local and institutional regulations) at the study site. Once drawn into syringes for administration, AZD1222 and saline placebo were not visually distinct from each other.

9.4.4 Treatment Compliance

The measures to ensure that the participant was compliant with treatment, and the criteria for acceptable compliance, can be found in Section 6.4 of the CSP (Appendix 16.1.1).

9.4.5 Pre-study, Concomitant, and Post-study Treatment(s)

Justification for pre-study and concomitant treatments or therapies that were allowed, restricted, or prohibited in this study can be found in Section 6.5 of the CSP (Appendix 16.1.1).

Other medication considered necessary for the participant's safety and well-being could be given at the discretion of the investigator(s). The administration of all medication (including study intervention) was recorded in eCRFs.

9.4.5.1 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant was receiving at the time of enrollment or receives during the period specified in the SoA (Section 9.1) must be recorded in the eCRF along with the information listed below. Vitamins and/or herbal supplements are not recorded.

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Study Physician was contacted if there were any questions regarding concomitant or prior therapy.

Permitted Concomitant Medications

Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after the last dose of study intervention. Licensed influenza vaccines are permitted at any time.

Prohibited Concomitant Medications

The following medications are prohibited, and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications and/or vaccines; however, does not definitively require withdrawal of the participant from the study, but may have determined a participant's eligibility to receive a second dose or evaluability in the PPS or IAS.

If a participant receives a prohibited concomitant medication, the investigator, in consultation with the Sponsor, evaluates any potential impact on receipt of study intervention based on time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication compromises the participant's safety or interpretation of the data (see Section 9.5).

- Investigational products indicated for the treatment of SARS-CoV-2 or COVID-19.
  Note: For participants who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted.
- Experimental vaccinations, other than AZD1222, for prevention of SARS-CoV-2 or COVID-19.
  Note: Participants choosing to receive a licensed and/or authorized COVID-19 vaccine should inform the investigator so it can be properly documented. Participants who receive a licensed and/or authorized COVID-19 vaccine outside the study should be encouraged to continue study conduct to be followed for safety reporting and all assessments.
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention (eg, first dose and second dose). Thirty days post second dose, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit.
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit.
- Immunoglobulins and/or any blood product.

9.4.5.2 Dose Modification

Study intervention was administered as described in Section 6.1.2 of the CSP (Appendix 16.1.1). Dose modification was not permitted.

9.4.5.3 Treatment After the End of the Study

There is no intervention after the end of the study.

9.5 Discontinuation from Study Treatment and Withdrawal from Study

Participants could discontinue the study intervention and can discontinue assessments at any time or at the discretion of the investigator(s). Specific reasons for discontinuation of study intervention and the procedures followed are listed in Section 9.5.1.

Participants who discontinued the study intervention were asked about the reason(s) for discontinuation from the study intervention and about the presence of any AEs. Additionally, it was documented whether they were to continue with other study assessments after study intervention was stopped. If possible, participants were seen and assessed by an investigator.

Participants are also free to withdraw from the study at any time, without prejudice to further treatment. Specific reasons for withdrawal of participants from this study, and the procedures to be followed when a participant withdraws or was incorrectly enrolled, are listed in Section 9.5.2. For participants who withdraw from the study, it should be noted whether they are assessed after withdrawal from the study, and they should be asked about the reason(s) for their withdrawal from the study and about the presence of any AEs. If possible, they are seen and assessed by an investigator.

In both of the above circumstances, AEs are followed, and any study materials are to be returned by the participant.

Where a participant did not meet all the eligibility criteria but incorrectly received study intervention, the investigator should have informed the Study Physician immediately, and a discussion should have occurred between the Study Physician and the investigator regarding whether to continue or discontinue the participant.

9.5.1 Discontinuation of Study Intervention

Each participant in the randomized, double-blinded phase should have received 2 doses of blinded study intervention (see Section 6 of the CSP [Appendix 16.1.1]). An individual participant did not receive the first or second dose of blinded study intervention if any of the following occurred in the participant in question:

1 Withdrawal of consent after signing informed consent
2 Participant met one or more of the exclusion criteria or failed to meet all inclusion criteria for study participation
3 Laboratory-confirmed SARS-CoV-2 infection
4 Participant was pregnant or nursing
5 Any allergic reaction, including anaphylaxis, that was assessed as related to study intervention
6 Any SAE assessed as related to study intervention

7 Any AE that, in the judgment of the site investigator, was related to study intervention and may have jeopardized the safety of the study participant
8 Receipt of a prohibited concomitant medication that may have jeopardized the safety of the study participant or interpretation of the data

Each participant who received at least 1 dose of study intervention is followed for the full study period unless consent is withdrawn specifically from further study participation, or the participant is lost to follow up. Participants who did not receive study intervention, regardless of reason, will not be followed.

9.5.2 Withdrawal from 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).
- 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 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 Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once protocol-specified sample analysis is complete.

9.6 Data Quality Assurance

Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in Appendix A7 of the CSP (Appendix 16.1.1).

The Sponsor's quality assurance and quality control procedures provide reassurance that the clinical study program is being carried out in accordance with GCP guidelines. The Sponsor undertook a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures are directed towards all aspects of the clinical study process and its associated documentation.

9.7 Study Measurements and Procedures

Section 9 of the CSP (Appendix 16.1.1) describes the methods used to measure study variables and the definitions of outcome variables. Details of the timing of the procedures (ie, the activities to be conducted at each visit) are contained in the study plan (see Section 9.1).

Table 10 presents the study endpoints and shows how they relate to the study objectives. Details of the timing of the procedures (ie, the activities to be conducted at each visit) are contained in the SoA (see Section 9.1).

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Primary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19	**Endpoint:** A binary response, whereby a participant with negative serostatus at baseline is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post dose 2 of study intervention. Otherwise, a participant is not defined as a COVID-19 case. **Intercurrent events**: For participants who withdrew from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawals was treated as missing (ie, counted as not having met the criteria); participants who withdrew before 15 days post dose 2 or who had a case prior to 15 days post dose 2 were excluded from the primary endpoint analysis. Participants unblinded to treatment assignment prior to having met the criteria for the primary efficacy endpoint were censored at the date of unblinding. **Summary measure:** VE, calculated as 1-relative risk. (Relative risk was the incidence in the vaccine group relative to the incidence in the control group.)	See CSP section 9.4.2.1 and/or SAP section 16.1.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Primary	Safety	To assess the safety and tolerability of 2 IM doses of AZD1222 compared to saline placebo	• Incidence of AEs for 28 days post each dose of study intervention • Incidences of SAEs, MAAEs, and AESIs from Day 1 post treatment through Day 730	See CSP section 9.4.3.1 and/or SAP section 18.1.
Primary	Safety	To assess the reactogenicity of 2 IM doses of AZD1222 compared to saline placebo (Substudy only) [a]	Incidences of local and systemic solicited AEs for 7 days post each dose of study intervention	See CSP section 9.4.3.1 and/or SAP section 18.1.
Secondary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of SARS-CoV-2 infection	The incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention [c]	See CSP section 9.4.2.2 and/or SAP section 16.2.1.1.
Secondary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of symptomatic COVID-19 using CDC criteria	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using CDC criteria	See CSP section 9.4.2.2 and/or SAP section 16.2.1.2.
Secondary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of University of Oxford-defined symptomatic COVID-19	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria	See CSP section 9.4.2.2 and/or SAP section 16.2.1.3.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Secondary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, regardless of evidence of prior SARS-CoV-2 infection [c]	See CSP section 9.4.2.2 and/or SAP section 16.2.1.4.
Secondary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of severe or critical symptomatic COVID-19	• The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention [c] • The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post first dose of study intervention	See CSP section 9.4.2.2 and/or SAP section 16.2.1.5.
Secondary	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related emergency department visits	The incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose of study intervention [c]	See CSP section 9.4.2.2 and/or SAP section 16.2.1.6.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Secondary	Immunogenicity	To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [a, b]	• Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies (MSD serology assay) • The proportion of participants who had a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay)	See CSP section 9.4.2.2 and/or SAP section 17.
Secondary	Immunogenicity	To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [a, b]	• Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay) • Proportion of participants who had a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay)	See CSP section 9.4.2.2 and/or SAP section 17.
Secondary	Efficacy	To estimate the efficacy of AZD1222 compared to saline placebo for the prevention of COVID-19 following the first dose	The incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention	See CSP section 9.4.2.2 and/or SAP section 16.2.1.7.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Exploratory	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the all-cause mortality	The incidence of all-cause mortality from Day 1 through Day 730	See SAP section 16.3.1.1.
Exploratory	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for COVID-19-related deaths	The incidence of COVID-19-related deaths occurring from Day 1 through Day 730	See SAP section 16.3.1.2.
Exploratory	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related hospitalizations	• The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention • The incidence of COVID-19-related hospitalizations occurring post first dose of study intervention	See SAP section 16.3.1.3.
Exploratory	Efficacy	To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related ICU admissions	• The incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention • The incidence of COVID-19-related ICU admissions occurring post first dose of study intervention	See SAP section 16.3.1.4.
Exploratory	Efficacy	To quantify SARS-CoV-2 viral loads in infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR	See SAP section 16.3.1.5.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Exploratory	Efficacy	To characterize sequence variations in SARS-CoV-2 through genotypic analyses in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	Genotypic analysis of SARS-CoV-2 from NP swabs collected on Day 1 Illness Visit	See CSP section 8.6.1.1 and/or SAP section 16.3.1.6.
Exploratory	Efficacy	To quantify duration of viral shedding in symptomatic SARS-CoV-2 infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	Duration of SARS-CoV-2 shedding in saliva over time	See CSP section 8.6.1.2 and/or SAP section 16.3.1.7.
Exploratory	Efficacy	To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with 2 IM doses of AZD1222 or saline placebo [d] (Illness Visits only) [b]	Biophysical parameters, including, but not limited to, serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from Illness Visits Day 1 through Day 28	See CSP section 8.2 and/or SAP section 16.3.1.8.
Exploratory	Efficacy	To assess symptoms associated with COVID-19 using an e-diary in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only) [b]	Symptoms recorded by participants in an Illness e-diary from Illness Visits Day 2 through Day 28	See CSP section 8.1.2.3 and/or SAP section 16.3.1.9.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Exploratory	Immunogenicity	To assess SARS-CoV-2 specific antibodies in an ACE2 competition assay following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only) [a, b d]	• Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ACE2 competing antibodies from serum samples • Proportion of participants who had a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) in ACE2 competing antibodies	See SAP section 17.1.
Exploratory	Immunogenicity	To assess B- and T-cell responses following 2 IM doses of AZD1222 or saline placebo (Substudy only) [a d]	• Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 S protein from day of dosing baseline to 14 days post each dose • Intracellular cytokine staining and flow cytometry for B- and T-cell responses from day of dosing baseline to 14 days post each dose	See CSP section 8.5.2.4 and/or SAP section 17.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Exploratory	Immunogenicity	To assess SARS-CoV-2 antibodies in nasal secretions following 2 IM doses of AZD1222 or saline placebo (Substudy only) [a d]	• Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in SARS-CoV-2 S, RBD, and Nucleocapsid antibodies (MSD serology assay) • Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to SARS-CoV-2 S, RBD, and Nucleocapsid antigens (MSD serology assay)	See CSP section 9.4.2.2 and/or SAP section 17.
Exploratory	Immunogenicity	To assess anti-vector responses to the ChAdOx1 adenovirus vector following 2 IM doses of AZD1222 or saline placebo (Substudy only) [a]	Proportion of participants who had a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to AZD1222 as measured by ChAdOx1 neutralizing antibodies	See CSP section 9.4.2.2 and/or SAP section 17.
Exploratory	Immunogenicity	To assess additional immune responses following 2 IM doses of AZD1222 or saline placebo [d]	Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data	See CSP section 9.4.2.3 and/or SAP section 17.
Exploratory	Safety	To assess the long-term safety and tolerability of 2 IM doses of AZD1222 [d]	Incidences of SAEs, MAAEs, and AESIs post first dose of AZD1222 through Day 730	See CSP section 9.4.2.3 and/or SAP sections 18.1.2, 18.1.6, and 18.1.7.

Table 10 Study Objectives and Variables

Objective			Endpoint/Variable	
Priority	**Type**	**Description**	**Description**	**Method of assessment and derivation**
Study objectives and variables reported in this interim CSR				
Exploratory	Efficacy	To assess the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19 [d]	The incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of AZD1222 through Day 360	See CSP section 9.4.2.3 and/or SAP sections 16.2.1.2 and 16.2.1.3.
Exploratory	Efficacy	To assess the durability of efficacy of 2 IM doses of AZD1222 against SARS-CoV-2 infection [d]	The incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of AZD1222 through Day 730	See CSP section 9.4.2.3 and/or SAP section 16.2.1.1.

[a] Substudy: The Substudy was conducted only in the USA. The first participants randomized in each age group in the USA, which included 1500 participants 18 to 55 years of age; 750 participants 56 to 69 years of age; and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.

[b] Illness Visits: Participants who presented with qualifying symptoms were tested for SARS-CoV-2 and, if positive, completed Illness Visits.

[c] Key secondary endpoint.

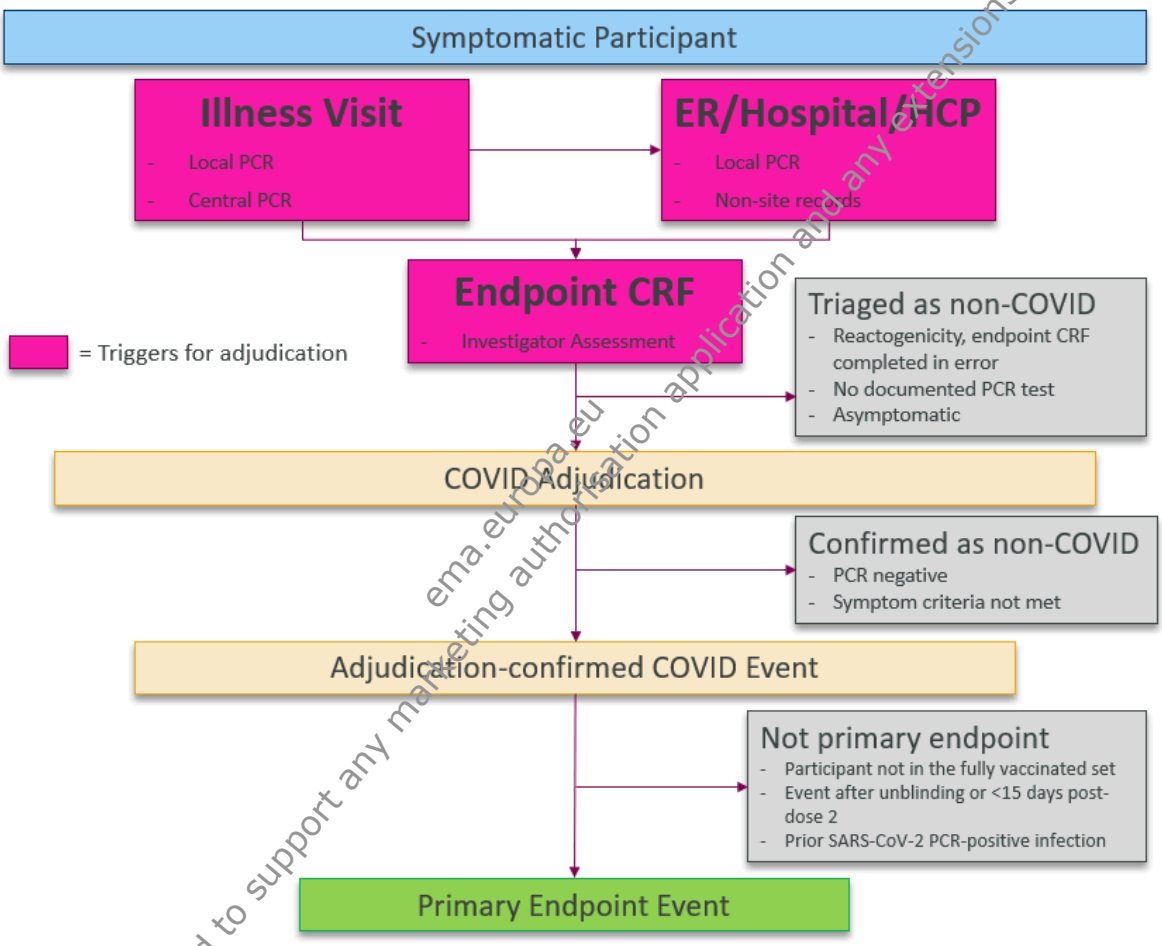
[d] For some exploratory endpoints, results are not yet available or are being assessed at the time of data cut-off date and are not included in the assessment of efficacy and immunogenicity summarized in this report.

ACE2 = angiotensin-converting enzyme 2; AE = adverse event; AESI = adverse event of special interest; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease-2019; CSP = Clinical Study Protocol; ELISpot = enzyme-linked immunospot; GMFR = geometric mean fold rise; GMT = geometric mean titer; ICU = intensive care unit; IFN-γ = interferon-gamma; IM = intramuscular; MAAE = medically attended adverse event; MSD = Meso Scale Discovery; NP = nasopharyngeal; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction, RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; S = Spike; SAE = serious adverse event; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America; VE = vaccine efficacy

Case Adjudication Process

A blinded independent efficacy endpoint adjudication committee assesses symptomatic participants (see Section 6.3.2). Figure 2 provides an overview of the case adjudication process and how this process relates to the derivation of the primary efficacy endpoint.

Figure 2 Case Adjudication Process for Study D8110C00001



COVID-19 = coronavirus disease 2019; CRF = case report form; ER = emergency; HCP = healthcare provider; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

The adjudication process is triggered when an Endpoint Reporting or COVID-related Hospitalization eCRF form is completed, or when an Illness Visit is recorded in the database. A participant narrative is generated programmatically by the IQVIA biometrics programming team that includes all relevant information from the eCRF, including local and central SARS-CoV-2 RT-PCR results, and is submitted to the Clinical Events Validation and Adjudication team at IQVIA responsible for the management of the adjudication process. Adjudicators also require hospital records and other relevant information, depending on the

specific details of the case. In some instances, as expected, the requirement of hospital records during this pandemic at times may result in prolonged adjudication, pending provision of the complete data set.

All individuals involved in sample and data handling as part of the adjudication process are blinded to treatment allocation. Data cleaning activities and monitoring are performed by IQVIA. This included queries to sites to ensure that Endpoint eCRFs are completed for all participants with Illness Visits, and a review of digital health device activations and illness e-diary data to ensure that all Illness Visits and local RT-PCR results are recorded in the eCRF. Medical review of AEs is performed to ensure that any COVID-19-related events are documented in the eCRF in the form of Illness Visits (where applicable) and Endpoint eCRFs.

With regard to whether a participant is considered positive for the SARS CoV-2 RT-PCR test, the central laboratory test result is used for the determination of a SARS-CoV-2-RT-PCR-positive result. In case the central laboratory result is not available, the local laboratory test result is used. In the event that the results of the local and central laboratory are discordant (ie, local result is positive and central result is negative), the result of the central saliva SARS-CoV-2-RT-PCR collected from the Illness Visit is considered.

A similar process is followed for all COVID-19 endpoints.

9.8 Statistical Methods and Determination of Sample Size

9.8.1 Statistical and Analytical Methods

A comprehensive SAP was prepared. All statistical evaluations, as well as summaries and tabulations, are performed by qualified personnel at IQVIA or ClinChoice. For more details of the statistical analyses, see Section 4 of the SAP (Appendix 16.1.9). Statistical analysis software (SAS®) Version 9.4 or higher is used to generate all statistical analyses, data summaries, and listings.

The following general principles apply throughout the study:

- For continuous data, descriptive statistics (ie, n [number of participants with available data], mean or geometric mean, SD or geometric standard deviation, median, minimum and maximum, and quartiles values) are presented by study arm and visit, when applicable.
- For categorical data, the number and percentage of participants in each category are presented by study arm and visit, when applicable. The denominator for percentage calculation is the underlying analysis set population unless otherwise stated.
- Baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention (including unscheduled assessments). In the case where the last non-missing measurement and the date and time of the first dose of study intervention coincided, that measurement is considered to be baseline, but AEs and medications

commencing on the date of the first dose of study intervention are considered post-baseline. Illness Visit baseline is defined as the first non-missing measurement taken on Illness Visit day 1. If there is no non-missing measurement available on Illness Visit day 1, Illness Visit baseline is considered as missing.

9.8.1.1 Multiple Comparisons/Multiplicity

The primary efficacy endpoint and 4 key secondary endpoints were to be assessed at 2 time points during the study, giving an interim analysis and a primary analysis. The pre-planned interim analysis was included to support early assessment of efficacy prior to reaching the 150 events required for the primary analysis. The interim and primary analyses were in close proximity and, as such, the results from the primary analysis are the focus of this report. For detailed description of the testing strategy at the interim analysis, see Section 7.4 of the SAP (Appendix 16.1.9).

A Lan-DeMets alpha-spending function was used to account for multiplicity of the primary endpoint across the 2 time points. Given that statistical significance was achieved at the interim analysis (see Section 9.8.4 for interim analysis results), the primary analysis presented estimates with nominal 2-sided 95% CI, and statistical significance was achieved if the 2-sided CI was > 30%. At the primary analysis, the success criterion for the study was nominally statistically significant, with an observed VE point estimate of at least 50%. If the primary endpoint achieved nominal statistical significance at the 5% level at the primary analysis, a hierarchical approach was used to control for multiplicity of the primary and key secondary efficacy endpoints. That is, the null hypotheses for these efficacy endpoints were tested in a hierarchical order, and the subsequent null hypothesis was tested at a nominal significance level of 5% (2-sided) at the primary analysis, only if the prior null hypothesis was rejected.

A formal assessment of the key secondary efficacy endpoints at the primary analysis was only conducted if the statistical significance of the primary efficacy endpoint was demonstrated at nominal 2-sided alpha of 5% at the primary analysis. Therefore, no further multiplicity adjustment was necessary.

For a detailed description of the testing strategy at the primary analysis, see Section 7.4 of the SAP (Appendix 16.1.9).

This study is conducted by multiple investigators at multiple centers internationally. Data from all centers are pooled together in the analyses, and there are no plans to perform an analysis of homogeneity of the results across centers.

9.8.1.2 Efficacy

COVID-19-related endpoints, including the primary endpoint, are based on case adjudication (see Section 9.7).

Primary Efficacy Endpoint

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention in a participant with negative serostatus at baseline. Participants are included in the primary endpoint if they have RT-PCR-confirmed SARS-CoV-2 and meet the following criteria at any point from their initial Illness Visit at the site (Day 1) through their second Illness Visit (Day 14):

1 One or more Category A findings

OR

2 Two or more Category B findings

Category A:

- Pneumonia diagnosed by chest x-ray or computed tomography scan
- Oxygen saturation of ≤ 94% on room air or requiring either new initiation or escalation in supplemental O_2
- New or worsening dyspnea/shortness of breath

Category B:

- Fever > 100 °F (> 37.8 °C) or feverishness
- New or worsening cough
- Myalgia/muscle pain
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhea (only one finding to be counted toward endpoint definition)
- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition)

Participants who are hospitalized with COVID-19 with no associated Illness Visit are included in the primary analysis if they matched the criteria based on the adjudication of hospital records. For participants with negative serostatus at baseline who died ≥ 15 days post second dose, if there was a SARS-CoV-2 RT-PCR-positive result from the central lab before death, the participant would have been considered as having met the primary endpoint; if there was not a SARS-CoV-2 RT-PCR-positive result from the central lab before death, but COVID-19 symptoms were identified and the participant had a SARS-CoV-2 RT-PCR-positive result from any lab, the participant would have been considered as having met the primary endpoint as well.

Primary analysis of primary efficacy endpoint

The primary efficacy analysis of the primary endpoint was performed on the FVS population. For participants who withdrew from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawals (or lost to follow up, death not caused by SARS-CoV-2) was treated as missing.

A Poisson regression model with robust variance (Zou 2004) adjusting for follow-up time was used as the primary efficacy analysis model to estimate the RR on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention between the AZD1222 and the placebo groups. The model contained the terms of study arm and age group at the time of informed consent (ie, ≥ 18 to < 65 years, and ≥ 65 years) as covariates. The logarithm of the participant's corresponding monitoring period at risk starting from 15 days post second dose of study intervention up to the data cut-off date was used as an offset variable in the model to adjust for participants having different exposure times during which the events occurred. Participants who withdrew or had a non-COVID-19 related death prior to having met the criteria for the primary efficacy endpoint were not counted as having the event, and the follow-up time for these participants was at that time from 15 days post second dose. Participants who (1) were unblinded to treatment assignment and (2) received authorized COVID-19 vaccine, in both cases prior to having met the criteria for the efficacy endpoint were not counted as having the event. Their follow-up time was censored at the date of unblinding/authorized COVID-19 vaccine administration, whichever was earlier. Calculation of follow-up time was detailed as follows:

- For participants who met the primary endpoint before the end of monitoring period, the follow-up time was calculated as (Date of Onset of Primary Endpoint) – (Date of Second Dosing + 14) + 1. Date of Onset of Primary Endpoint was defined as the collection date of a central lab positive COVID-19 test, or local lab if central was not available.
- For participants who did not experience a primary endpoint event before the end of monitoring period, the efficacy follow-up time was determined based on the following:
  - If a SARS-CoV-2 RT-PCR positive symptomatic or asymptomatic event not meeting the primary endpoint criteria occurred during the COVID-19 monitoring period, the efficacy follow-up time was calculated as (Date of Positive COVID-19 Test) – (Date of Second Dosing + 14) + 1.
  - If an end of study date occurred during the COVID-19 monitoring period, the efficacy follow-up time was calculated as (Date of End of Study) – (Date of Second Dosing + 14) + 1.
  - If an end of study date occurred after the COVID-19 monitoring period, the efficacy follow up was censored at the end of COVID-19 monitoring period.

For participants who continued to participate in the study at the time of primary analysis, the data cut-off date was used as their last assessment date. Vaccine efficacy, which was the

incidence in the vaccine group relative to the incidence in the control group expressed as a percentage, was calculated as RRR = 1- RR. Relative risk reduction and its corresponding nominal 2-sided 95% CI was estimated from the Poisson regression model with robust variance. In addition, the 2-sided p-value testing null hypothesis that the VE was equal to 30% was obtained from the model. Statistical significance was achieved if the 95% CI for VE was > 30%. The success criterion for the study is nominal statistical significance with an observed VE point estimate of at least 50%.

The Poisson regression with robust variance analysis was implemented by using the SAS PROC GENMOD procedure with the REPEATED statement for participant identification and logarithm link as well as OFFSET option. The estimated parameter $\hat{\beta}$ [ie, $\log(\widehat{RR})$], nominal 2-sided 95% CI for $\hat{\beta}$, and the 2-sided p-value are obtained from the SAS outputs. The estimated RR and corresponding CI for the RR is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of RRR is given by [1 – exp($\hat{\beta}$) * 100%]. The CI for the percent of RRR is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

If the number of participants in any stratum is too small and/or convergence cannot be achieved with the Poisson regression analysis model, the model is reduced to exclude the age group covariate. If convergence is not achieved by excluding the age group covariate, a stratified Exact Poisson Regression model is used as the primary analysis model to test the treatment effect on SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD1222 and placebo groups. The number of events for each combination of treatment and strata is used as the response variable. The logarithm of total number of participants for each combination of treatments and strata is used as an offset variable in the model. The Exact Poisson Regression test is stratified by age group at the time of informed consent (ie, ≥ 18 to < 65 years, and ≥ 65 years). The SAS procedure of PROC GENMOD with EXACT statement is used to perform the analysis. The RR of AZD1222 over placebo for the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention and the 95% CI is obtained from the SAS procedure. The percent of RRR and the 95% CI is reported following the relationship of RRR (%) = (1- RR) * 100%. In the event that active study arm has 0 events and placebo has ≥ 1 event, the MLE for the RR is zero, corresponding to VE = 100%, however, PROC GENMOD gives a median unbiased estimate instead of the MLE, and the upper confidence limit of VE cannot be estimated in this extreme situation. In such cases, the VE was set to the MLE (100%) and the 1-sided 97.5% CI is presented for completeness. The inverse is treated similarly when there are 0 events in the placebo arm and ≥ 1 event in the active arm, such that the VE is set to - Infinity and the 1-sided CI is presented.

The numbers and percentages of participants with SARS-CoV-2 RT-PCR-positive symptomatic illness were also presented for the following intervals: participants prior to

15 days post first dose, between 15 days post first dose and prior to second dose, between second dose and 15 days post the second dose, between 15 days post second dose and prior to month 6, between month 6 and month 12, overall, post first dose.

For detailed description of the interim analysis of primary efficacy endpoint, see Section 16.1.3 of the SAP (Appendix 16.1.9).

Sensitivity analysis for primary efficacy endpoint

As a sensitivity analysis to the handling of missing data in the analysis of the primary efficacy endpoint, the primary analysis of the primary efficacy endpoint was repeated with multiple imputation for intercurrent events, without using log follow-up time as offset. For participants who were in the FVS but (1) did not have a SARS-CoV-2 RT-PCR-positive symptomatic illness status occurring ≥ 15 days post second dose of study intervention and withdrew from the study prior to the time of analysis, or (2) were in the FVS and were unblinded to treatment assignment prior to having met the criteria for the efficacy endpoint or (3) received authorized COVID-19 vaccine prior to having met the criteria for the efficacy endpoint, their event status was imputed assuming the observed event rate per treatment group conditional on stratification factor using multiple imputation techniques, as described in the following paragraphs.

The primary analysis using Poisson regression with robust variance required a participant level dataset. A repeated imputation approach was introduced to impute the status of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention for missing observations at the participant-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and CI estimation of the treatment effect was expected through the repeated imputation (Little and Rubin 2002). In the primary analysis, the missing outcome for participants with censored follow up (eg, study withdrawal, lost to follow up, death not caused by SARS-CoV-2, unblinding/authorized COVID-19 vaccination) prior to reaching cut-off time for analysis without a SARS-CoV2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention was imputed per age group stratum using the event rate for the treatment group. The imputation and subsequent analysis was carried out using SAS PROC MI (Monotone Logistic Regression Method) and SAS PROC MIANALYZE. The detailed imputation steps are described in Section 16.1.4 of the SAP (Appendix 16.1.9).

Additional sensitivity analyses were carried out using multiple imputation as described above using the placebo event rate for their event status.

Supplementary analyses for primary efficacy endpoint

To support the primary analysis, a Cox PH model using the same covariates as for the primary analyses as well as Kaplan-Meier curves was presented for the active and control groups

based on observed events, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention. Time to event, ie, the duration in days since 15 days post second study dose to event or censoring, was fit using the PH model with study arm as a factor and age group as stratum. Hazards ratios for each study arm along with the nominal 2-sided 95% CI was obtained from the PH model. The number of participants with primary endpoint and the number of censored participants was also provided. The censoring timing at each month was displayed.

The primary analysis was repeated on the PPS as a supplementary analysis. The same 2-sided p-value testing null hypothesis that the VE is equal to 30% was presented.

Another supplementary analysis was to break down the primary analysis described above, by repeating it for events occurring < 6 months from first dose of study intervention and ≥ 6 months from the first dose of study intervention up to the end of the COVID-19 monitoring period to show the efficacy over time. Note: As the median follow up time post second dose for this data cut-off date was 2 months, no events in either study intervention arm were recorded in the ≥ 6 months' time period; hence, data from this analysis is not included in this report.

Additionally, the primary analysis was repeated, excluding participants with out-of-window vaccination due to the clinical hold, ie, participants who received their first dose of study intervention between 28 August 2020 and 06 September 2020 (for additional detail, see Section 7.4).

The primary analysis was repeated and included participants in the FVS who (1) were unblinded to treatment assignment or (2) received authorized COVID-19 vaccine, in both cases prior to having met the criteria for the efficacy endpoint. Censoring at study unblinding or authorized COVID-19 vaccine administration was not performed.

Subgroup analyses for primary efficacy endpoint

Subgroup analysis is performed for the primary efficacy endpoint, SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention. For subgroup analyses, the FVS was used, except for the subgroup analysis for serostatus at baseline, which used the FVS regardless of baseline serostatus. Treatment-by-subgroup interaction was tested using the Poisson regression with robust variance model adjusting for follow-up time with the terms of treatment, age group, subgroup, and treatment-by-subgroup interaction, which was implemented using PROC GENMOD procedure. If this full model did not achieve convergence, a reduced model of treatment, subgroup, and treatment-by-subgroup interaction was used. Within each level of a subgroup, the RRR and its corresponding 95% CI was estimated using a Poisson regression model with

robust variance with the term of treatment, age group at informed consent, and adjusted for follow-up time. A forest plot of the RRR and the 95% CI was presented.

The subgroup analysis was conducted for the subgroups as described in Section 9.8.2.1, provided there were sufficient events observed for each subgroup level. In the case of sparse data for one or more levels of a subgroup, alternative analysis approaches may have been used, such as combining subgroup levels or fitting separate models for each subgroup.

For subgroups corresponding to one of the stratification factors included in this analysis model, the corresponding factor was not included in the model.

Secondary Endpoints

The set of secondary endpoints included the following summary measures:

- Incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention (key secondary endpoint)
- Incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using CDC criteria (see Section 8.1.1 of the CSP [Appendix 16.1.1] for definition)
- Incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria. Cases were defined as RT-PCR-confirmed SARS-CoV-2 and having at least one of the following symptoms:
  1 New onset of fever (> 100 °F [> 37.8 °C]), OR
  2 Cough, OR
  3 Shortness of breath, OR
  4 Anosmia/ageusia
- Incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, regardless of evidence of prior SARS-CoV-2 infection (key secondary endpoint)
- Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic COVID-19 occurring ≥ 15 days post second dose of study intervention (see Section 8.1.1 of the CSP [Appendix 16.1.1] for definition) (key secondary endpoint)
- Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic COVID-19 occurring post first dose of study intervention
- Incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose of study intervention (key secondary endpoint)
- The incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention

Following the same methodology outlined for the primary endpoint, each of the key secondary endpoints were analyzed by a separate Poisson regression model with robust variance (Zou 2004), including study arm and age as covariates, according to the hierarchical approach for multiplicity protection.

For non-key secondary endpoints, the same methodology outlined for the primary endpoint was applied. A p-value, corresponding to a 2-sided test, was presented to compare the vaccine against the control. The p-value was nominal as non-key secondary endpoints were not controlled for multiplicity. To support these analyses, descriptive statistics were produced for the vaccine and control groups.

Exploratory Endpoints

The exploratory endpoints were:

- The incidence of all-cause mortality occurring from Day 1 through Day 730.
- The incidence of COVID-19-related deaths occurring from Day 1 through Day 730.
- The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention.
- The incidence of COVID-19-related hospitalizations occurring post first dose of study intervention.
- The incidence of COVID 19-related ICU admissions occurring ≥ 15 days post second dose of study intervention.
- The incidence of COVID-19-related ICU admissions occurring post first dose of study intervention.
- Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR (Illness Visits only).
- Genotypic analysis of SARS-CoV-2 from NP swabs collected on Day 1 Illness Visit (Illness Visits only).
- Duration of SARS-CoV-2 shedding in saliva over time (Illness Visits only).
- Symptoms recorded by participants in an illness e-diary from Illness Visits Day 2 through Day 28 (Illness Visits only).

An overview of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose is provided and included:

- Number of Illness Visits
- Number of SARS-CoV-2 RT-PCR-positive results for each visit.

These summaries were repeated for the following intervals: second dose date + 15 days to < 6 months from the dose 1 date and ≥ 6 months from dose 1 date to end of COVID-19 monitoring period. Note: As the median follow up time post second dose for this data cut-off

date was 2 months, no events in either study intervention arm were recorded in the ≥ 6 months' time period; hence, these summaries are not included in this report.

9.8.1.3 Safety

The safety of AZD1222 was primarily assessed by:

- Incidence of AEs for 28 days post each dose of study intervention
- Incidence of SAEs from Day 1 post treatment through Day 730
- Incidence of MAAE (defined in Section 8.3.8 of the CSP [Appendix 16.1.1]) from Day 1 post treatment through Day 730
- Incidence of AESIs (defined in Section 8.3.9 of the CSP [Appendix 16.1.1]) from Day 1 post treatment through Day 730
- Incidences of local and systemic solicited AEs for 7 days post each dose of study intervention (Substudy only)

There were also other safety endpoints such as vital signs.

All safety summaries were presented by study arm based on the SAF. There were no statistical comparisons between the study arms for safety data.

For participants who were unblinded to treatment assignment during the study or received authorized COVID-19 vaccine, the unblinding/authorized COVID-19 vaccine administration was treated as an intercurrent event. Safety data collected during the unblinded/post-authorization COVID-19 vaccine administration follow up period were excluded from all summaries directly comparing the AZD1222 and placebo study arms, using exposure-adjusted rates to account for differences in duration of double-blinded follow up for SAEs, MAAEs, and AESIs which are collected through the full 2-year study period. Serious adverse events, MAAEs, and AESIs were summarized for the double-blinded period, unblinded period/post authorized COVID-19 vaccine period, and overall, separately for each study arm.

Summary statistics of follow-up time, as well as number and percentage of participants at risk at each month post first study intervention were provided for the SAF. This summary included the follow-up time post first dose as well as the follow-up time post second dose.

Adverse events

All AEs are considered unsolicited AEs (collected by 'open question' at study visits) unless they were categorized as solicited AEs recorded in the Substudy only (for further detail see Section 8.3.7 of the CSP [Appendix 16.1.1] and Section 18.2 of the SAP [Appendix 16.1.9]).

Non-serious AEs were recorded for 28 days post each dose of study intervention.
Serious AEs, MAAEs, and AESIs are recorded from the time of signature of the ICF through the last participant contact.

All AEs are coded using the MedDRA dictionary, version 23.1.

Unless specified, event summary referred to the summary of number of participants with the corresponding AE.

All AE summary tables listed below were repeated respectively for participants who were seronegative at baseline and participants who were seropositive at baseline.

Overall summaries of number and percentage of participants and number of events with the following AE categories were provided by study arm based on the SAF:

- All AEs
- All SAEs
- Related AEs by severity
- Related SAEs
- AEs leading to discontinuation from study intervention
- Related AEs leading to discontinuation from study intervention
- AEs leading to study discontinuation
- Related AEs leading to study discontinuation
- MAAEs
- AEs with outcome of death
- AESIs

Should a participant experience multiple events within a category, the participant was counted only once for that category.

An overall summary of number and percentage of participants and number of events within each of the categories described above was provided for the period from 1 to 28 days post any dose by study arm based on the SAF.

Exposure-adjusted rate was calculated as the number of participants with AEs in the categories above/total patient-years exposure to investigational study intervention. Participant years was determined by summing the total number of follow-up days of each participant, and then dividing by 365.25. The exposure period was calculated from time of first intervention to the end of the study.

Severity for AEs was classified as mild, moderate, or severe (increasing severity) by using FDA Grading for AEs (FDA 2007). For additional detail on summaries of AEs, SAEs, AEs leading to discontinuation (study intervention and/or study), death, and MAAEs, see Section 18.1 of the SAP.

Adverse events of special interest

Adverse events of special interest were events of scientific and medical interest specific to the further understanding of the study intervention safety profile and required close monitoring and rapid communication by the investigators to the sponsor. Adverse events of special interest for AZD1222 were based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience and scientific interest. See Appendix 7 of the SAP for a listing and description of AZD1222 AESIs.

In addition, the following AE analyses are presented:

Nervous system disorder adverse events

A summary of adverse events in the SOC of Nervous System Disorders by PT and study arm was prepared, including exposure-adjusted rates. Should a participant have experienced multiple events of the same PT, the participant was counted only once for that PT. Adverse events in the SOC of Nervous System Disorders were also summarized by baseline serostatus, age group, sex, and race. These events are also summarized for the double-blinded period, unblinded period/post-authorized COVID-19 vaccine administration, and overall, separately for each study arm.

The above summaries were repeated for the following:

- Vascular Disorders of Embolism and Thrombosis.
- Potentially Immune-Mediated Conditions (see Appendix 7)
- Standard MedDRA Queries (SMQs):
  - Demyelination
  - Peripheral neuropathy
  - Guillain-Barre Syndrome
  - Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
  - Immune mediated/autoimmune disorders
  - Anaphylactic reaction
  - Hypersensitivity

For participants in the Substudy, safety was assessed daily for 7 days after vaccination via an e-diary collection of solicited AEs. Solicited AEs should not have been reported as unsolicited AEs. Solicited AEs could have been reported as SAEs or MAAEs if they fulfilled the

protocol-defined criteria as such (see Section 8.3 of the CSP). Participants were instructed to record the timing and severity of local and systemic solicited AEs for 7 days following administration of each dose of study intervention, if applicable, and whether medication was taken to relieve the symptoms. These included local events (pain, tenderness, redness/erythema, swelling) and systemic events (fever [body temperature > 100 °F or 37.8 °C], chills, muscle pains, fatigue, headache, malaise, nausea, and vomiting). Severity was assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007). Each solicited AE was summarized at the following time intervals: overall during the interval Days 1 to 7, and daily during the interval Days 1 to 7 (individually). Additional details can be found in Section 18.2 of the SAP and Section 8.3.1 of the CSP.

For more details and additional safety endpoints, see the SAP (Appendix 16.1.9).

9.8.1.4 Immunogenicity

Unless otherwise indicated, all immunogenicity summaries are presented by study arm and visit (visits from Substudy and separately for visits from Illness Visits), when appropriate, based on the IAS.

For all immunogenicity endpoints, participants were censored at the date of unblinding/authorized COVID-19 vaccine administration, whichever occurred first, such that data from all visits after the date of unblinding/authorized COVID-19 vaccine administration are excluded from derivations and all by-visit summaries. All immunogenicity data, regardless of unblinding/authorized COVID-19 vaccine administration, are listed for all participants, with unblinded/authorized COVID-19 vaccine administration assessments flagged. For the assessment of durability of humoral immunogenicity, the data will be censored at the time of authorized COVID-19 vaccine administration and not at unblinding.

For summaries over time in participants from the Substudy, participants who did not receive a second dose of study intervention were excluded from all time points post second dose.

Secondary Immunogenicity Endpoints

The set of secondary immunogenicity endpoints are:

- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies (MSD serology assay) (Substudy and Illness Visits only)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay) (Substudy and Illness Visits only)

- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay) (Substudy and Illness Visits only)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value (see Section 17.1.3 of the SAP) to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudoneutralization assay) (Substudy and Illness Visits only)

Analysis of immunogenicity endpoints

The GMTs and GMFRs are calculated for the vaccine and control groups and are summarized at each scheduled visit (see Section 1.3 of the CSP [Appendix 16.1.1]). Descriptive statistics for GMTs and GMFRs include number of participants, geometric mean, 95% CI, minimum and maximum.

The GMT and GMFR endpoints are analyzed using an analysis of variance model which includes the log base 2-transformed value of titer (or log base 2-transformed value of fold rise for GMFR) as the dependent variable and study arm and age group as factors. On the log scale, the models are used to estimate a mean response for the vaccine and control groups and the difference (vaccine - control), with corresponding 95% CIs. These values are then back-transformed to give geometric means for the vaccine and control groups and a ratio of geometric means (vaccine/control), with corresponding 95% CIs. A p-value, corresponding to a 2-sided test, is presented to compare the vaccine against the control. The p-value is nominal as secondary endpoints are not controlled for multiplicity. This analysis is performed on participants who are seronegative at baseline (ie, participants having a titer value < lower limit of quantitation at baseline).

Seroresponse is a binary outcome where a success is when the fold rise in titers compared to baseline is ≥ 4. Seroresponse is calculated for the vaccine and control groups and is summarized at each scheduled visit (see Section 1.3 of the CSP [Appendix 16.1.1]).

The number and percentage of participants with post-vaccination seroresponse and 95% CIs are provided, and the 95% CI of seroresponse rate is calculated using the Clopper-Pearson exact method. These seroresponse summaries for serum samples of SARS-CoV-2 S, RBD, and Nucleocapsid antibodies as well as SARS-CoV-2 neutralizing antibodies, are also performed separately by baseline serostatus. Additionally, summaries for participants in the Substudy are presented by age group (18 to 64 years, ≥ 65 years) and by clinical hold status (randomized prior to clinical hold, randomized after clinical hold).

Exploratory Immunogenicity Endpoints

The exploratory immunogenicity endpoints are:

- Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in SARS-CoV-2 S, RBD, and Nucleocapsid antibodies in nasal secretions (MSD serology assay) (Substudy only). Note: Data from this analysis will be reported in an addendum to this CSR following the 6-month median follow up analysis.
- Proportion of participants who have a post treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to SARS-CoV-2 S, RBD, and Nucleocapsid antigens in nasal secretions (MSD serology assay) (Substudy only).
- Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ChAdOx1 neutralizing antibodies (Substudy only).
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to AZD1222 as measured by ChAdOx1 neutralizing antibodies (Substudy only).

Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data and will be described in a separate document.

9.8.2 Description of Analysis Sets

The populations defined in this study are presented in Table 11.

Table 11 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to use for reporting disposition and screening failures.
FAS	All randomized participants who received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study. Participants were analyzed according to their randomized study intervention irrespective of whether or not they prematurely discontinued, according to the intent-to-treat principle. Participants who withdrew consent to participate in the study were included up to the date of their study withdrawal.
FVS	The fully vaccinated analysis set included all participants in the full analysis set who were seronegative at baseline, received 2 doses of study intervention, and who remained on-study 15 days after their second dose without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection.
PPS	The per-protocol analysis set included participants in the fully vaccinated analysis set who received the correct dose of randomized study intervention and who did not have a serious protocol deviation. Detailed criteria defining this analysis set were documented in the SAP. Erroneously-treated participants who received one dose of active study intervention and one dose of saline placebo, regardless of the sequence, were excluded from this analysis set.
SAF	The safety analysis set consisted of all participants who received at least one dose of study intervention. Erroneously-treated participants who received one dose of active study intervention and one dose of saline placebo were accounted for in this analysis set by assigning them to the study intervention they actually received. A participant who had on one or several occasions received active study intervention was classified as active for all summaries, including summaries by dose.
IAS	The immunogenicity analysis population included all participants in the safety analysis set who had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response. Examples of protocol violations were documented in the SAP.

COVID-19 = coronavirus disease 2019; FAS = full analysis set; FVS = fully vaccinated analysis set; IAS = immunogenicity analysis set; PPS = per-protocol analysis set; RT-PCR = reverse transcriptase polymerase chain reaction; SAF = safety analysis set; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2.

9.8.2.1 Examination of Subgroups

The subgroups analyzed were:

- Age group at informed consent (≥ 18 to < 65 years and ≥ 65 years)
- Gender (male and female)
- Serostatus at baseline (negative and positive), where seropositive is defined by a positive Nucleocapsid antibody level as measured by Roche Elecsys Anti-SARS-CoV-2 serology test
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- COVID-19 comorbidities at baseline (at least one comorbidity, no comorbidity), where comorbidity risk factors included:
  - chronic kidney disease
  - chronic obstructive pulmonary disease
  - lower immune health because of transplant
  - history of obesity
  - serious heart condition
  - sickle cell disease
  - type 2 diabetes
  - asthma
  - dementia
  - cerebrovascular disease
  - cystic fibrosis
  - high blood pressure
  - liver disease
  - scarring in lungs (pulmonary fibrosis)
  - type 1 diabetes
  - thalassemia
  - history of smoking

9.8.3 Determination of Sample Size

Approximately 33000 participants were screened such that approximately 30000 participants were randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp) AZD1222 (the active group, n = approximately 20000) or saline placebo (the control group, n = approximately 10000) 4 weeks apart.

Note: 'Enrolled' meant 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 were screened for the purpose of determining eligibility for the study but were not randomly assigned/assigned in the study, were considered 'screen failures', unless otherwise specified by the CSP.

The sample size calculations are based on the primary efficacy endpoint and are derived following a modified Poisson regression approach (Zou 2004). The calculations account for an interim and primary analysis, and the timing of these analyses are driven by the number of events observed in the study. A Lan-DeMets alpha-spending function is used to account for multiplicity across the interim and primary analyses, such that the overall Type I error was controlled at 5%. The calculations assumed minimal loss to follow up as it was anticipated that participants would remain engaged in the study. All participants are followed for the entire duration of the study.

For the primary efficacy analysis, approximately 150 events meeting the primary efficacy endpoint definition were required across the active and placebo groups within the population of participants who were seronegative at baseline to detect a VE point estimate of 60% with > 90% power. These calculations assumed an observed event rate of approximately 0.8% and were based on a 2-sided test, where the lower bound of the 2-sided 95.10% CI for the VE point estimate was required to be greater than 30% with an observed point estimate of at least 50%.

A complete description and justification of the methods used to determine the planned sample size, together with their derivations or the reference source, is provided in Section 9.2 of the CSP (Appendix 16.1.1).

9.8.4 Interim Analyses

The interim efficacy analysis (including the primary efficacy endpoint and key secondary endpoint of severe or critical COVID-19) was conducted by an independent statistics group providing support to the DSMB. The interim analysis was planned to be conducted when approximately 75 events meeting the primary endpoint definition (ie, when approximately 50% of the total amount of statistical information was available) had been reported across the active and control groups within the population of participants who were seronegative at baseline. The interim analysis was used to support early assessment of efficacy and cumulative safety based on the available data. Detail of the interim analysis is described in the DSMB plan, but methodology was consistent with that described in the SAP.

The interim analysis was based on 141 events meeting the primary endpoint definition across the active and control groups within the population of participants who were seronegative at baseline. Based on 141 out of 150 cases occurring at the interim analysis, the alpha level used

was 4.16% according to the Lan-DeMets alpha spending function. The VE estimate was 78.9% (95.84% CI: 69.4, 85.4; Appendix 16.1.9). The DSMB determined that the efficacy and safety had been established based on review of the interim efficacy analysis and the cumulative safety data; therefore, a decision was made by the Oversight Group and URC to proceed with a regulatory submission based on the results of the interim analysis data cut (details are provided in the URC charter). Personnel from the Sponsor and its representatives (including IQVIA) associated with the analyses and regulatory submission of interim results were unblinded. At the time when the DSMB confirmed that efficacy and safety had been established, the case milestone for the primary analysis had been achieved (approximately 150 events meeting the primary endpoint definition across the AZD1222 and placebo groups); therefore, the primary analysis was performed, and the full set of interim analyses (beyond what was provided to the DSMB) were not performed. Only the primary analysis is presented in this report.

9.8.5 Data Monitoring Committees

The following committees are involved in data monitoring for the study:

- A PSRT comprised of Sponsor, COVID-19 Prevention Network, Biomedical Advanced Research and Development Authority, and NIAID medical officers is convened to oversee blinded safety surveillance of participants during the study.
- A COVID-19 Vaccine DSMB organized by the National Institutes of Health, NIAID, and comprised of independent experts is convened to provide unblinded oversight, to ensure safe and ethical conduct of the study. The COVID 19 Vaccine DSMB facilitated the interim analysis for safety and efficacy and has the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment is continuously monitored by the COVID-19 Vaccine DSMB to ensure that the balance remains favorable.
- An independent blinded Neurological AESI Expert Committee is available to review and provide advice to the PSRT and the COVID-19 Vaccine DSMB on request about the diagnosis and causality assessment of selected neurological AESIs occurring in the AZD1222 clinical development program.
- A blinded independent efficacy adjudication committee reviews relevant data of potential cases for the COVID-19-related efficacy endpoint evaluations.

See Appendix A5 of the CSP (Appendix 16.1.1) for further details about the data monitoring committees and see Appendix 16.1.9 for the detailed DSMB charter and names of DSMB members.

9.9 Changes in the Conduct of the Study or Planned Analyses

9.9.1 Clinical Study Protocol Amendments and Other Changes in the Conduct of the Study

All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an IRB/IEC.

Substantial changes in the conduct of the study that were implemented by CSP amendments are shown and briefly described in Table 12. Clinical Study Protocol Amendments 1 and 2 did not implement any substantial changes in the conduct of the study, and CSP Amendment 5 was not implemented; see Appendix 16.1.1 for full details of all CSP amendments.

Table 12 Substantial Protocol Amendments Related to Changes in Study Conduct

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
Amendments made *after* the start of participant recruitment		
Amendment 3 26 Oct 2020	Revised important potential risks	To align with information in the updated AZD1222 IB
	Increased the sample size from 30000 to 40000 participants	Increased based on updated attack rates and public health emergency
	Added a description of the independent Neurological AESI Expert Committee	New committee to provide advice on selected neurological AESIs
	Expanded the AESI list and specified that AESIs will be reported to the Sponsor within one day of becoming aware of the event	To permit close monitoring and rapid communication of safety information, and further understanding of the AZD1222 safety profile
	New section for evaluation of potential neurological AESIs	For additional safety monitoring
Amendment 4 14 Dec 2020	Revised the first secondary endpoint	To permit formal statistical comparison and inclusion as key secondary endpoint
	Identified the 4 key secondary endpoints (added footnote c)	To indicate these are the endpoints that are multiplicity protected
	Added an immunogenicity cohort of approximately 300 participants	To expand upon cell-mediated immunity data
	Reduced the sample size from 40000 back to the original number of 300000	Based on the efficacy already seen in the pooled analysis from the Oxford studies, and the large outbreak in the United States has increased the attack rate

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
	Added text to indicate that experimental vaccinations, other than AZD1222, for prevention of SARS-CoV-2 or COVID-19 are prohibited. Also, noted that participants who choose to receive an authorized COVID-19 vaccine should inform the Investigator so it can be properly documented, and they should be encouraged to continue study conduct.	To exclude experimental vaccinations other than AZD1222 and to allow participants access to emerging standard of care given the rapidly evolving COVID-19 vaccines landscape
	Specified the procedures for unblinding in the event a study participant is contacted about receiving an authorized COVID-19 vaccine	Clarification provided due to recent EUA for COVID-19 vaccines
	Specified that if the primary endpoint results of the interim or primary analysis are statistically significant, an additional analysis with 5% alpha will be performed once all participants have completed the first year of follow up	To evaluate long-term efficacy based on 1 year of follow up before the final analysis
	Revised to indicate how the primary efficacy endpoints and 4 key secondary endpoints will be assessed	To address the Agency's request for having a secondary endpoint testing strategy
Amendment 6 19 Feb 2021	Removed "and Adolescents" from the title and removed text from the study rationale regarding adolescents	Given removal of adolescents from the study population
	Upgraded exploratory endpoint 5 to secondary endpoint 9	To gain information on efficacy following a single dose of AZD1222
	Removed all references to Part 1 and Part 2 (Parts 1 and 2 were introduced in Amendment 5; an amendment which was not implemented)	Given removal of Part 2 from the protocol (Part 2 was introduced in Amendment 5; an amendment which was not implemented)
Amendment 7 29 Mar 2021	Revised to reflect the addition of an unblinded phase with an open-label dosing option (Part B). The original randomized, double-blind part of the study was labeled as Part A	To allow participants still blinded as to their original study intervention assignment (AZD1222 or placebo) to be unblinded so that those who previously received 1 or 2 doses of placebo or only 1 dose of AZD1222 can be offered open-label dosing of AZD1222
	Added additional exploratory objectives to assess the long-term safety and tolerability of 2 IM doses of AZD1222, the durability of efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19, and the durability of efficacy of 2 IM doses of AZD1222 against SARS-CoV-2 infection	Additional exploratory objectives added for safety and efficacy data

Note: This table presents only protocol amendments that were implemented and included substantial changes to the study design and/or conduct.

AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; EUA = Emergency Use Authorization; IB = Investigator's Brochure; IM = intramuscular; SARS-CoV-2 = severe acute respiratory syndrome-associated coronavirus

Additional changes in the conduct of the study are listed below:

- Participant unblinding to receive a COVID-19 EUA vaccine outside the study occurred starting on 10 Dec 2020, when the first COVID-19 vaccine received an EUA approval.
- At the time of reporting, AZD1222 has not received EUA approval by the FDA and > 90% of participants have been unblinded to confirm their randomized treatment arm; therefore, the decision was made to not implement Part B (open-label dosing) for the study.
- There were 170 participants with 302 AEs (all were nonserious) that were recorded in the solicited e-diary (start date > 7 days post dose), which should have been recorded as unsolicited AEs as per protocol. These participants were inadvertently allowed to record solicited symptoms in the e-diaries up to 28 days and hence, were incorrectly recorded in the e-diary as solicited AEs.
- There were 172 participants who were not part of the Substudy who were incorrectly provided with an e-diary. Of these, 164 participants recorded nonserious reactogenicity AEs.
- There were 158 participants who were unable to record solicited AEs for 7 days due to technical issues with the e-diary and/or site staff procedures. The solicited events for the impacted participants were instead recorded in the AE eCRF and summarized with the unsolicited AEs.
- Six sites unblinded a total of 1634 participants outside of the protocol-specified IRT system. The 6 sites utilized on-site pharmacy records to unblind participants without documenting in the IRT system. All unblinding events were corrected to reflect in the IRT system, and appropriate protocol deviations were issued.
- Intensity categories for solicited AE categories of erythema and swelling were defined as: Mild: 2.5 to 5 cm, Moderate: 5.1 to 10 cm, Severe: > 10 cm. Due to limitations in the e-diary, the maximum measurement possible to be recorded was > 6 cm. Hence, results > 6 cm were displayed in the combined category "Moderate/Severe".

9.9.2 Changes to Planned Analyses

Analyses conducted in addition to pre-specified SAP analyses are described in Table 13. This table indicates when any changes were made in relation to the unblinding of study data.

Table 13 Changes to Planned Analyses

Key details of change	Reason for change	SAP amendment?
Changes made before unblinding of study data		
Summary of follow-up time by age group as well as the summary of follow-up time by dosing interval and age group.	Health authority request	No
Additional subgroups evaluated for the primary efficacy endpoint including by individual comorbidities, age by comorbidity categories, BMI, and number of comorbidities.	Health authority request	No
Key secondary endpoints evaluated by subgroups.	To ensure complete understanding of efficacy by important subgroups.	No
All unsolicited adverse event summaries are repeated for the following subgroups: age group, sex, race, comorbidities, and age by comorbidities.	Health authority request	No
Nonserious AE and related nonserious AE summaries are included, overall and by subgroups.	Health authority request	No
Grade 3 or higher AE and related Grade 3 or higher AE summaries are included, overall and by subgroups.	Health authority request	No
Related MAAE summaries are included, overall and by subgroups.	For completeness, other AE summaries are repeated for related events.	No
Additional summaries of adverse events (described in Section 18.1.8 of the SAP) are repeated in the following subgroups; comorbidities and age by comorbidities.	Health authority request	No
Solicited AE summaries are repeated in the following subgroups: sex, race, comorbidities, and age by comorbidities.	Health authority request	No
The dosing interval was calculated for the FVS.	Dosing interval summary was repeated for FVS for completeness.	N/A

Key details of change	Reason for change	SAP amendment?
Changes made after unblinding of study data		
An updated data extraction was performed on 29 April 2021 (based on the same data cut-off date of 05 March 2021) and the primary analysis was updated.	The primary analysis was conducted, per CSP, from a data extraction performed on 19 March 2021, based on a data cut-off date of 05 March 2021. A total of 190 adjudicated events met the primary endpoint definition. This analysis was consistent with the CSP and SAP. The high-level results from the primary analysis were shared with the DSMB and included in a corporate press release on 25 March 2021. Approximately 14 potential events meeting the primary endpoint criteria that occurred prior to the data cut-off date had not yet completed the adjudication process. Therefore, an updated data extraction was performed on 29 April 2021, based on the same data cut-off date of 05 March 2021, to ensure that all potential events had completed adjudication, all pending laboratory results were available, and any data cleaning that occurred between 19 March 2021 and 29 April 2021 could be incorporated into an updated analysis, which are presented in this document as the "updated primary efficacy analysis."	N/A
Frequency of SARS-CoV-2 variants was investigated by whole genome sequencing in saliva samples to assess variants by lineages (and clades) and next generation sequencing of the Spike protein from NP swabs to assess the individual amino acid changes observed in the Spike protein.	To provide additional data on SARS-CoV-2 variants.	N/A
Vaccine efficacy of variants was also evaluated using FVS for those adjudicated cases of COVID-19 that occurred ≥ 15 days post second dose of study.	The VE estimates against variants emerged as an important aspect of efficacy.	N/A
Cumulative incidence of clearance for shedding for cases occurring ≥ 15 days post second dose was evaluated for the IAS and FVS.	Viral shedding during breakthrough infections have critical implications for pandemic control; data after first dose (IAS) and in FVS were investigated for completeness.	N/A
MSD Spike antigens and nAb quantitation over time by race, ethnicity, and participants that experienced the clinical hold was evaluated in the IAS (seronegative at Baseline).	To expand upon immunogenicity in important subpopulations.	N/A

Key details of change	Reason for change	SAP amendment?

AE = adverse event; BMI = body mass index; COVID-19 = coronavirus disease-2019; CSP = clinical study protocol; DSMB = Data Safety Monitoring Board; FVS = fully vaccinated set; IAS = immunogenicity analysis set; MAAE = medically attended adverse event; MSD = Meso Scale Discovery; N/A = not applicable; nAb = neutralizing antibodies; NP = nasopharyngeal; SAP = statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

10. STUDY PARTICIPANTS

Summary tables and figures pertaining to this section are presented in Section 14.1 (Table 14.1.1.1 to Table 14.1.8.2) and Appendix 16.2.4.

10.1 Disposition

The disposition of the participants in this study is summarized in Figure 3 and Table 14 below.

A summary of disposition by serostatus at Baseline is provided for the all participants analysis set (see Table 14.1.1.2). Summaries of enrollment by country, or by country and baseline serostatus, are also provided for the all participants analysis set (see Table 14.1.5.1 and Table 14.1.5.2, respectively).

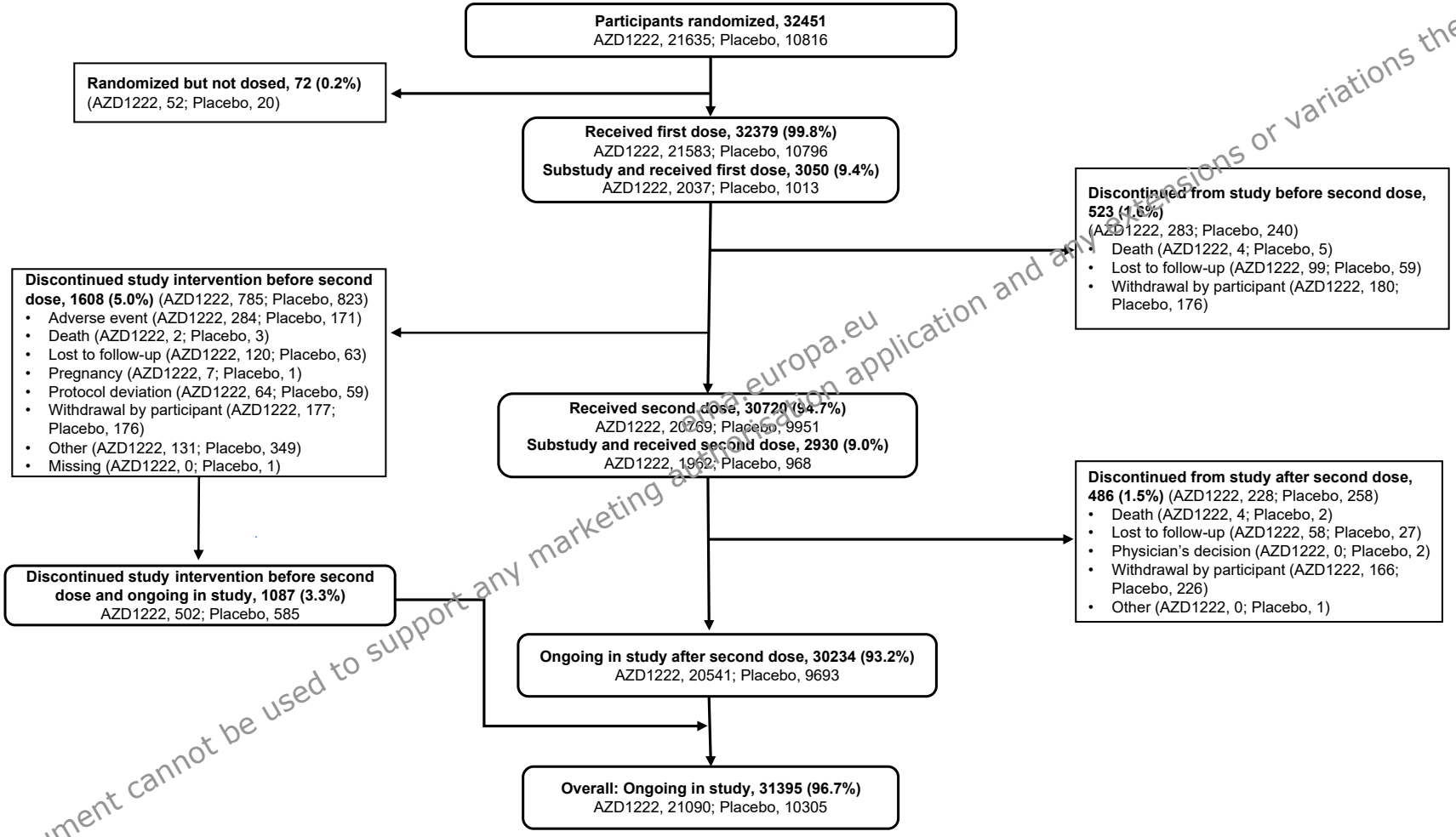
As of the cut-off date of 05 March 2021, 32379 participants had been randomized and received at least one dose of study intervention (21583 received AZD1222 and 10796 received placebo) (ie, included in the all participants analysis set) (Table 14). Nearly all (96.7%) participants were ongoing in the study at the time of the data cut-off date (21090 [97.5%] participants in the AZD1222 group and 10305 [95.3%] in the placebo group). The percentage of participants who had discontinued from the study was 3.3%, and the most common reasons were withdrawal by participant (362 participants [66.4% of those who discontinued] in the AZD1222 group, 408 [79.8% of those who discontinued] in the placebo group) and lost to follow up (157 participants [28.8% of those who discontinued] in the AZD1222 group, 86 [16.8% of those who discontinued] in the placebo group).

Overall, a total of 5.0% (1608 of 32451 participants) discontinued from study intervention. The most common reasons were other (131 participants [16.7% of those who discontinued] in the AZD1222 group and 349 participants [42.4% of those who discontinued] in the placebo group), AE (284 participants [36.2% of those who discontinued] in the AZD1222 group, 171 participants [20.8% of those who discontinued] in the placebo group), and withdrawal by participant (177 participants [22.5% of those who discontinued] in the AZD1222 group, 176 participants [21.4% of those who discontinued] in the placebo group). Note: “other” included discontinuations due to availability of authorized COVID19 EUA vaccines. Participants in the AZD1222 group were more likely to receive their second dose of study

intervention after unblinding, while placebo participants were not expected to receive a second placebo dose and instead elect to receive an EUA vaccine.

Overall, a small percentage of participants discontinued from the study prior to receiving their second dose (1.6%) and after receiving their second dose (1.5%) (Table 14). Overall, the most common reasons for study discontinuation prior to and after receiving the second dose were withdrawal by participant (68.1% and 80.7%, respectively) and lost to follow up (30.2% and 17.5%, respectively) (Table 14). In the ≥ 18 to < 65 years age group, 1.7% of the participants discontinued from the study prior to receiving their second dose, and 1.5% participants discontinued from the study after receiving their second dose. Overall, the most common reasons for study discontinuation in this age group prior to and after receiving the second dose were withdrawal by participant 64.2% and 76.3%, respectively) and lost to follow up (34.7% and 21.9%, respectively). In the ≥ 65 years age group, 1.4% of the participants discontinued from the study prior to receiving their second dose and 1.5% participants discontinued from the study after receiving their second dose. Overall, the most common reason for study discontinuation in this age group prior to and after receiving the second dose was withdrawal by participant (84.8% and 95.5% respectively) (Table 14.1.1.3). For further details on discontinuations of study intervention due to AEs in the SAF, see Section 12.3.4.

Figure 3 Participant Disposition (All Participants Analysis Set)



Source: Table 14.1.1.1 and Table 14.1.3

Table 14 Participant Disposition (All Participants Analysis Set)

	AZD1222 N=21635 n (%)	Placebo N=10816 n (%)	Total N=32451 n (%)
Full analysis set	21583 (99.8)	10796 (99.8)	32379 (99.8)
Fully vaccinated set	17662 (81.6)	8550 (79.0)	26212 (80.8)
Per-protocol analysis set	17534 (81.0)	8337 (77.1)	25871 (79.7)
Safety analysis set (as randomized)	21583 (99.8)	10796 (99.8)	32379 (99.8)
Immunogenicity analysis set	21581 (99.8)	10785 (99.7)	32366 (99.7)
Participants in Substudy	2037 (9.4)	1013 (9.4)	3050 (9.4)
Participants screened*	NA	NA	34301
Participants screen-failed [a]±	NA	NA	1842 (5.4)
Participants randomized	21635	10816	32451 (94.6)
Participants randomized but not dosed	52 (0.2)	20 (0.2)	72 (0.2)
Participants who completed the study	0	0	0
Participants who are ongoing in study	21090 (97.5)	10305 (95.3)	31395 (96.7)
Discontinued from study	545 (2.5)	511 (4.7)	1056 (3.3)
Reason for Discontinuation [b]			
Withdrawal by participant	362 (66.4)	408 (79.8)	770 (72.9)
Lost to follow up	157 (28.8)	86 (16.8)	243 (23.0)
Protocol deviation	18 (3.3)	7 (1.4)	25 (2.4)
Death	8 (1.5)	7 (1.4)	15 (1.4)
Physician decision	0	2 (0.4)	2 (0.2)
Other	0	1 (0.2)	1 (<0.1)
Participants who received first dose	21583 (99.8)	10796 (99.8)	32379 (99.8)
Ongoing in study after first dose	21072 (97.4)	10298 (95.2)	31370 (96.7)
Discontinued study before second dose	283 (1.3)	240 (2.2)	523 (1.6)
Reason for discontinuing early from study prior to second dose [b]			
Withdrawal by participant	180 (63.6)	176 (73.3)	356 (68.1)
Lost to follow up	99 (35.0)	59 (24.6)	158 (30.2)
Death	4 (1.4)	5 (2.1)	9 (1.7)
Discontinued study intervention	785 (3.6)	823 (7.6)	1608 (5.0)
Reason for discontinuation of study intervention [b]			
Other	131 (16.7)	349 (42.4)	480 (29.9)
Adverse event	284 (36.2)	171 (20.8)	455 (28.3)
Withdrawal by participant	177 (22.5)	176 (21.4)	353 (22.0)
Lost to follow up	120 (15.3)	63 (7.7)	183 (11.4)
Protocol deviation	64 (8.2)	59 (7.2)	123 (7.6)
Pregnancy	7 (0.9)	1 (0.1)	8 (0.5)
Death	2 (0.3)	3 (0.4)	5 (0.3)
Missing	0	1 (0.1)	1 (<0.1)

	AZD1222 N=21635 n (%)	Placebo N=10816 n (%)	Total N=32451 n (%)
Participants who discontinued study intervention and are ongoing	502 (2.3)	585 (5.4)	1087 (3.3)
Participants who received second dose	20769 (96.0)	9951 (92.0)	30720 (94.7)
Ongoing in study	20541 (94.9)	9693 (89.6)	30234 (93.2)
Discontinued study after second dose [b]	228 (1.1)	258 (2.4)	486 (1.5)
Reason for discontinuing early from study			
Withdrawal by participant	166 (72.8)	226 (87.6)	392 (80.7)
Lost to follow up	58 (25.4)	27 (10.5)	85 (17.5)
Death	4 (1.8)	2 (0.8)	6 (1.2)
Physician decision	0	2 (0.8)	2 (0.4)
Other	0	1 (0.4)	1 (0.2)
Participants unblinded [c] after second dose	7635 (35.3)	4157 (38.4)	11792 (36.3)

[a] Percentages were based on the number of screened participants.

[b] Percentages were based on the number of randomized participants who discontinued.

[c] Included unblinding to study intervention or receiving authorized COVID-19 vaccine, whichever was earlier.

*: 184 participants were rescreened and are counted twice. A total of 34117 unique participants were screened.

±: 181 participants were screen failures at one occasion. A total of 1661 unique participants were screen failures.

Note: Percentages were based on the number of randomized participants by study arm, unless otherwise noted.

Note: One participant was enrolled at two separate sites under two participant identification numbers PPD and PPD . This participant was randomized at both sites and received both doses of study intervention. This participant was included in the all participants analysis set but was excluded from all other analysis sets.

Note: Three participants were erroneously randomized twice. The participant numbers associated with dosing PPD PPD PPD were assigned to the randomized participants analysis set. Study participant numbers PPD PPD PPD not associated with dosing were excluded from the randomized participants analysis set.

Note: Four study participants were screened and not randomized but they did not appear as screen failures in the CRF.

COVID-19 = coronavirus disease-2019; CRF = case report form; NA = not applicable.

Sources: Tables 14.1.1.1 and 14.1.3

10.2 Protocol Deviations

For the summary of number of participants with important protocol deviations in each treatment group for the all randomized participants set, see Table 14.1.2.

A total of 3161 study participants (9.7%) had at least 1 important protocol deviation and included 1851 participants (8.6%) in the AZD1222 group and 1310 participants (12.1%) in the placebo group. The most common important protocol deviation was deviation from protocol that resulted in failure to collect data related to safety, data integrity, or key endpoints (2139 total participants) and occurred in a similar proportion of study participants across the AZD1222 and placebo groups (6.5% and 6.8%, respectively).

An imbalance was observed between study intervention arms in terms of not adhering to concomitant medication restrictions, with a higher proportion in the placebo group compared with the AZD1222 group (5.4% vs 1.2%, respectively). Review of these deviations in the placebo group showed that the majority were due to the participant receiving a concomitant medication (another EUA vaccine) within 30 days post study intervention dose. A greater number of participants who received placebo, once unblinded, decided to receive an approved EUA vaccine. However, if they received another EUA vaccine within the 30-day post study dosing window, they were in violation of the CSP for this study. As a result, this imbalance was expected.

Participants with important protocol deviations are listed, by center, in Appendix 16.2.2.

10.3 Study Participants Analyzed (Analysis Sets)

The analysis sets and the number of participants in each analysis set and reasons for exclusion are summarized in Table 15 below. Definitions of the analysis sets are given in Section 9.8.2.

As of the cut-off date of 05 March 2021, 32379 randomized participants received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study; and were included in the FAS. Of these, 26212 participants were seronegative at baseline, received 2 doses of study intervention, and remained on-study 15 days after their second dose without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection; and were included in the FVS. Of the FVS, 25871 participants received the correct dose of randomized study intervention and did not have a serious protocol deviation; and were included in the PPS.

A total of 32379 participants received at least one dose of study intervention and were included in the SAF. Of these, 32366 participants had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response; and were included in the IAS. Of the SAF, 3050 participants were included in the Substudy (3050 participants had received one dose of study intervention and 2930 participants had received both doses of study intervention).

The percentages of participants in the FAS and SAF were similar between the AZD1222 and placebo groups.

Table 15 Primary Analysis Populations

Analysis Set	AZD1222 N=21635 n (%)	Placebo N=10816 n (%)	Total N=32451 n (%)
Full analysis set[a]	21583 (99.8)	10796 (99.8)	32379 (99.8)
Reason for exclusion			
Not dosed	52 (0.2)	20 (0.2)	72 (0.2)
Fully vaccinated analysis set [b]	17662 (81.6)	8550 (79.0)	26212 (80.8)
Reason for exclusion			
Did not receive two doses	866 (4.0)	865 (8.0)	1731 (5.3)
Had a positive, missing or indeterminate serostatus at baseline	1046 (4.8)	516 (4.8)	1562 (4.8)
Followed for less than 15 days post second dose	2206 (10.2)	920 (8.5)	3126 (9.6)
SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection prior to 15 days post second dose	73 (0.3)	69 (0.6)	142 (0.4)
Per-protocol analysis set [c]	17534 (81.0)	8337 (77.1)	25871 (79.7)
Reason for exclusion			
Not in fully vaccinated analysis set	3973 (18.4)	2266 (21.0)	6239 (19.2)
Received the incorrect dose of randomized study intervention	9 (<0.1)	4 (<0.1)	13 (<0.1)
Serious protocol deviation	274 (1.3)	587 (5.4)	861 (2.7)
Participants included in the safety analysis set (as randomized)[d]	21587 (99.8)	10792 (99.8)	32379 (99.8)
Reason for exclusion			
Not dosed	52 (0.2)	20 (0.2)	72 (0.2)
Participants included in the immunogenicity analysis set [e]	21581 (99.8)	10785 (99.7)	32366 (99.7)
Reason for exclusion			
Not dosed	52 (0.2)	20 (0.2)	72 (0.2)
Exclusionary protocol deviation	7 (<0.1)	7 (<0.1)	14 (<0.1)
Participants included in the Substudy [f]	2037 (9.4)	1013 (9.4)	3050 (9.4)
Substudy safety analysis set – received first dose	2037 (9.4)	1013 (9.4)	3050 (9.4)
Substudy safety analysis set – received second dose	1962 (9.1)	968 (8.9)	2930 (9.0)
Participants excluded from all analyses	52 (0.2)	20 (0.2)	72 (0.2)
Reason for exclusion			
Not dosed	52 (0.2)	20 (0.2)	72 (0.2)

[a] The full analysis set included all randomized participants who received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study. Participants were classified according to the study intervention they were randomized to.

[b] The fully vaccinated analysis set which was a subset of the full analysis set that included participants who were seronegative at baseline, received 2 doses of randomized treatment and followed for at least 15 days post second dose without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection.

[c] The per-protocol analysis set included participants in the fully vaccinated analysis set who received the correct dose of randomized study intervention (both doses) and who did not have a serious protocol deviation.

[d] The safety analysis set included all participants who received at least one dose of study intervention.

[e] The immunogenicity analysis set included all participants in the safety analysis set who had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response. Participants were classified according to the study intervention they actually received.

[f] Participants were classified according to the study intervention they actually received.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: Serostatus at baseline was defined by the Nucleocapsid antibody level as measured by Roche Elecsys Anti-SARS-CoV-2 serology test.

Note: Reasons for exclusion were not mutually exclusive.

Note: Three participants were erroneously randomized twice. The participant numbers associated with dosing PPD PPD PPD were assigned to the randomized participants analysis set. Participant numbers PPD PPD PPD not associated with dosing were excluded from the randomized participants analysis set.

COVID-19 = coronavirus disease-2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

Source: Table 14.1.3

10.4 Demographic and Other Participant Characteristics

The demographic and key baseline characteristics of study participants in the FVS are summarized in Table 16. The demographic and key baseline characteristics of study participants in the SAF were similar to those of the FVS (see Table 14.1.4.1).

The demographic characteristics in the FVS were generally similar among participants who received AZD1222 and placebo (Table 16).

For the FVS, the mean age of participants was 49.9 years and the majority (79.0%) of the participants were aged 18 to 64 years, with 21.0% of participants aged ≥ 65 years. Overall, 56.3% were male, 79.2% were White, 23.3% were Hispanic or Latino, 87.3% were in the USA, and the mean BMI was 28.7 kg/m^2.

At least one protocol-defined high-risk condition for severe COVID-19 was present in 59.1% of participants (Table 17). The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 (see Section 9.8.2.1 for the list of comorbidity risk factors).

For the SAF, 30889 of total participants (95.4%) were seronegative at baseline, and 915 participants (2.8%) were seropositive, with similar proportions between study intervention groups (see Table 14.1.4.1). The remaining participants had either missing

serostatus (177 participants [0.5%]) or the assessment was not performed (398 participants [1.2%]).

Table 16 Demographic and Other Baseline Characteristics (Fully Vaccinated Analysis Set)

	AZD1222 N=17662	Placebo N=8550	Total N=26212
Age (years), n	17662	8550	26212
Mean (SD)	49.8 (15.73)	49.9 (15.71)	49.9 (15.73)
Median	51.0	51.0	51.0
Min, max	18, PPD	18, PPD	18, PPD
Age, subgroups (years)	17662	8550	26212
Category 1, n	17662	8550	26212
≥ 18 to < 65 years, n (%)	13966 (79.1)	6738 (78.8)	20704 (79.0)
≥ 65 years, n (%)	3696 (20.9)	1812 (21.2)	5508 (21.0)
Category 2, n	17662	8550	26212
≥ 18 to < 56 years, n (%)	10564 (59.8)	5071 (59.3)	15635 (59.6)
≥ 56 to < 70 years, n (%)	5245 (29.7)	2578 (30.2)	7823 (29.8)
≥ 70 years, n (%)	1853 (10.5)	901 (10.5)	2754 (10.5)
Category 3, n	17662	8550	26212
≥ 18 to < 65 years, n (%)	13966 (79.1)	6738 (78.8)	20704 (79.0)
≥ 65 to < 75 years, n (%)	3006 (17.0)	1476 (17.3)	4482 (17.1)
≥ 75 years, n (%)	690 (3.9)	336 (3.9)	1026 (3.9)
Sex, n	17662	8550	26212
Male, n (%)	9922 (56.2)	4829 (56.5)	14751 (56.3)
Female, n (%)	7740 (43.8)	3721 (43.5)	11461 (43.7)
Ethnicity, n	17662	8550	26212
Hispanic or Latino, n (%)	4035 (22.8)	2064 (24.1)	6099 (23.3)
Not Hispanic or Latino, (n%)	13351 (75.6)	6370 (74.5)	19721 (75.2)
Not reported, n (%)	238 (1.3)	106 (1.2)	344 (1.3)
Unknown, n (%)	38 (0.2)	10 (0.1)	48 (0.2)
Race [a], n	17662	8550	26212
Multiple n (%)	421 (2.4)	202 (2.4)	623 (2.4)
White, n (%)	14011 (79.3)	6755 (79.0)	20766 (79.2)
Black or African American, n (%)	1401 (7.9)	706 (8.3)	2107 (8.0)
Asian, n (%)	747 (4.2)	352 (4.1)	1099 (4.2)
American Indian or Alaska Native, n (%)	744 (4.2)	373 (4.4)	1117 (4.3)
Native Hawaiian or Other Pacific Islander, n (%)	50 (0.3)	14 (0.2)	64 (0.2)
Not reported, n (%)	207 (1.2)	110 (1.3)	317 (1.2)
Unknown	81 (0.5)	38 (0.4)	119 (0.5)

	AZD1222 N=17662	Placebo N=8550	Total N=26212
Weight (kg) n	17476	8479	25955
Mean (SD)	84.44 (21.125)	84.82 (21.390)	84.56 (21.213)
Median	81.70	81.90	81.80
Min, max	PPD	PPD	PPD
Height (cm), n	17472	8471	25943
Mean (SD)	171.25 (10.002)	171.34 (9.895)	171.28 (9.967)
Median	171.45	171.80	171.45
Min, max	PPD	PPD	PPD
BMI (kg/m^2), n	17468	8471	25939
Mean (SD)	28.70 (6.446)	28.80 (6.533)	28.73 (6.475)
Median	27.50	27.70	27.60
Min, max	PPD	PPD	PPD
BMI Category (kg/m^2), n	17468	8471	25939
≤ 30, n (%)	11576 (66.3)	5541 (65.4)	17117 (66.0)
> 30, n (%)	5892 (33.7)	2930 (34.6)	8822 (34.0)
Country, n	17662	8550	26212
United States, n (%)	15435 (87.4)	7443 (87.1)	22878 (87.3)
Chile, n (%)	1360 (7.7)	672 (7.9)	2032 (7.8)
Peru, n (%)	867 (4.9)	435 (5.1)	1302 (5.0)
Comorbidities, n	17661	8549	26210
Yes	10376 (58.8)	5105 (59.7)	15481 (59.1)
No	7285 (41.2)	3444 (40.3)	10729 (40.9)
Exposure risk to COVID-19 per OSHA categories, n	17459	8442	25901
Very high exposure, n (%)	965 (5.5)	456 (5.4)	1421 (5.5)
High exposure, n (%)	3741 (21.4)	1676 (19.9)	5417 (20.9)
Medium exposure, n (%)	7547 (43.2)	3654 (43.3)	11201 (43.2)
Lower exposure, n (%)	5206 (29.8)	2656 (31.5)	7862 (30.4)

[a] Participants who reported more than one race were reported under 'Multiple.'

Note: Age, in years, was relative to the date of signed informed consent.

Note: Percentages were based on the number of participants with available data (n) in the analysis set by study arm.

Note: Baseline was defined as the last non-missing measurement taken prior to the first dose of study intervention (including unscheduled measurements, if any).

Note: COVID-19 Comorbidities at baseline = Yes if any pre-defined comorbidity was Yes.

BMI = body mass index; COVID-19 = coronavirus disease-2019; max = maximum; min=minimum; OSHA = Occupational Safety and Health Administration; SD = standard deviation.

Source: Table 14.1.4.5

Table 17 provides the proportions of participants with pre-defined comorbidities based on presence or absence of CDC risk factors for severe COVID-19 disease. The characteristics were generally similar among participants who received AZD1222 and placebo. The presence

of these pre-defined risk factors was assessed at screening. Overall, 59.1% of participants had at least one comorbidity, and the proportion of participants with comorbidities in each treatment arm was similar. The most common comorbidities were a history of obesity (27.2%), high blood pressure (26.6%), a history of smoking (19.1%), and asthma (10.0%).

Table 17 Summary of Pre-defined Comorbidities at Baseline (Fully Vaccinated Analysis Set)

	AZD1222 N=17662 n (%)	Placebo N=8550 n (%)	Total N=26212 n (%)
Any pre-defined COVID-19 comorbidity at baseline	10376 (58.8)	5105 (59.7)	15481(59.1)
History of obesity (BMI > 30)	4735 (26.8)	2387 (27.9)	7122 (27.2)
High blood pressure	4712 (26.7)	2262 (26.5)	6974 (26.6)
History of smoking	3359 (19.0)	1655 (19.4)	5014 (19.1)
Asthma	1727 (9.8)	890 (10.4)	2617 (10.0)
Type 2 diabetes	1228 (7.0)	662 (7.7)	1890 (7.2)
Serious heart conditions	567 (3.2)	258 (3.0)	825 (3.1)
Liver disease	268 (1.5)	132 (1.5)	400 (1.5)
Chronic obstructive pulmonary disease	238 (1.3)	142 (1.7)	380 (1.4)
Cerebrovascular diseases	173 (1.0)	85 (1.0)	258 (1.0)
Chronic kidney disease	129 (0.7)	43 (0.5)	172 (0.7)
Type 1 diabetes	100 (0.6)	60 (0.7)	160 (0.6)
Thalassemia	29 (0.2)	17 (0.2)	46 (0.2)
Scarring in the lungs (pulmonary fibrosis)	28 (0.2)	10 (0.1)	38 (0.1)
Dementia	6 (< 0.1)	7 (< 0.1)	13 (< 0.1)
Sickle cell disease	5 (< 0.1)	5 (< 0.1)	10 (< 0.1)
Lower immune health because of a solid organ transplant	5 (< 0.1)	2 (< 0.1)	7 (< 0.1)

Note: Baseline was defined as the last non-missing measurement taken prior to the first dose of study intervention (including unscheduled measurements, if any).
Note: Percentages were based on the number of participants with available data (n) in the analysis set by study arm.
BMI = body mass index; COVID-19 = coronavirus disease-2019.
Source: Table 14.1.6.3

The following summaries of demographic and other baseline characteristics, comorbidities, medical history, and concomitant or prior medication were also performed and are provided as indicated (for definitions of analysis sets, see Section 9.8.2):

- Demographic and other baseline characteristics
  - By serostatus at baseline using the SAF (Table 14.1.4.2.1)
  - By country using the SAF (Table 14.1.4.2.2)

  - Using the IAS (Table 14.1.4.3)
  - By serostatus at baseline using the IAS (Table 14.1.4.4)
  - Using the SAF - Substudy (Table 14.1.4.6)
  - Using the IAS - Substudy (Table 14.1.4.7)
- Baseline comorbidities
  - Using the SAF (Table 14.1.6.1)
  - By serostatus at baseline using the SAF (Table 14.1.6.2)
- Medical History using the SAF (Table 14.1.7.1)
- Concurrent conditions/illnesses using the SAF (Table 14.1.7.2)
- Medications
  - Prior medications using the SAF (Table 14.1.8.1)
  - Concomitant medications using the SAF (Table 14.1.8.2)

10.5 Use of Concomitant Medication and Treatment Compliance

10.5.1 Concomitant Medication after Study Entry

For the SAF, concomitant medications (> 10% of participants in either group) during the study are provided in Table 14.1.8.2.

A total of 27063 participants (83.6%) received at least 1 concomitant medication during the study. All concomitant medications during the study were generally balanced between both treatment groups, with the exception of COVID-19 EUA vaccines; 1392 participants (6.4%) in the AZD1222 group received EUA vaccines compared with 2892 participants (26.8%) in the placebo group (Table 14.1.8.2).

10.5.2 Treatment Compliance

Compliance was not calculated because participants were vaccinated within the clinics. For more details, see Section 9.4.4. For extent of exposure, see Section 12.1.

As of the data cut-off date of 05 March 2021, 32379 (99.8%) participants had received at least one dose of study intervention with 21583 participants receiving AZD1222 (Table 14). A total of 30720 participants (94.7%) had received 2 doses of study intervention, with 20769 participants receiving AZD1222.

Table 18 summarizes the interval between dose 1 and dose 2 of study intervention overall, and separated for participants randomized prior to the clinical hold and participants randomized after removal of the clinical hold for all participants who received 2 doses of study intervention.

The median dosing interval was 29.0 days for both study intervention groups using the overall SAF and when limited to those participants who were randomized after removal of the clinical hold. Of note, 516 participants in the AZD1222 group and 259 participants in the placebo group were randomized prior to the initiation of the clinical hold, resulting in median dosing intervals of 60.0 days and 59.0 days, respectively. The maximum dosing interval due to the clinical hold was 148 days (approximately 21 weeks) for the AZD1222 group and 154 days (22 weeks) for the placebo group.

Using the FVS, the median dosing interval was 29.0 days for both study intervention groups, and the majority of participants in the AZD1222 and placebo groups received their second dose within the CSP allowable window of ≥ 26 days to ≤ 36 days (95.7% and 95.3% of participants, respectively; see IEMT Table 388).

Table 18 Dosing Interval (Safety Analysis Set)

Dosing Interval (days)	Statistic	AZD1222 N=21587	Placebo N=10792
Overall	n	20773	9947
	Mean (SD)	30.4 (5.65)	30.5 (5.80)
	Median	29.0	29.0
	Min, max	19, 148	22, 154
Participants randomized prior to the clinical hold	n	516	259
	Mean (SD)	60.6 (5.72)	60.7 (7.51)
	Median	60.0	59.0
	Min, max	53, 148	54, 154
Participants randomized after the clinical hold	n	20257	9688
	Mean (SD)	29.6 (2.83)	29.7 (2.82)
	Median	29.0	29.0
	Min, max	19, 99	22, 102

Note: The participants randomized prior to the clinical hold were those who received their first dose of study intervention between 28 August 2020 and 06 September 2020.
Note: The dosing interval (in days) was calculated as the date of dose 2 – date of dose 1 +1.
Max = maximum; Min = minimum; SD = standard deviation.
Source: Table 14.1.9.1.

Summary tables and figures pertaining to this section are presented in Appendix 16.2.5.

10.6 Conclusions on Study Participants

- The demographics and key baseline characteristics were representative of the intended population and were well-balanced between the AZD1222 and placebo groups:
  - The mean age of participants at screening was 49.9 years, and the majority of participants (79.0%) were 18 to 64 years of age, with 21.0% of participants ≥ 65 years of age.
  - The gender ratio between the AZD1222 and placebo groups was balanced (43.8% female vs 43.5% female, respectively).
  - The majority of participants were White (79.2%); 23.3% were Hispanic or Latino.
  - The majority of participants were in the USA (87.3%); 7.8% were in Chile and 5.0% were in Peru.
  - Most participants (95.4%) were seronegative at baseline.
  - Overall, 59.1% of participants had at least one comorbidity, and the proportion of participants with comorbidities in each treatment arm was similar; the most common comorbidities were obesity, high blood pressure, a history of smoking, and asthma.
- For participants randomized prior to the initiation of the clinical hold, the median dosing interval between dose 1 and dose 2 of study intervention was longer (60.0 days for participants in the AZD1222 group and 59.0 days for participants in the placebo group) than for participants randomized after removal of the clinical hold (29.0 days each for participants in the AZD1222 group and in the placebo group).
- The percentage of participants who discontinued from the study was 3.3%, and the most common reasons were withdrawal by participant (66.4% of those who discontinued in the AZD1222 group and 79.8% of those who discontinued in the placebo group) and lost to follow up (28.8% of those who discontinued in the AZD1222 group and 16.8% of those who discontinued in the placebo group).
- The incidence of important protocol deviations was low (9.7%) and balanced between treatment groups. The nature of the deviations did not suggest an impact to the overall conduct of this study or the interpretation of the study results.

11. EFFICACY EVALUATION

11.1 Efficacy Results

The interim efficacy analysis was conducted on the 141 events meeting the primary endpoint definition in the active and control groups within the population of participants included in the FVS (see Appendix 16.1.9). The DSMB determined that efficacy had been established based on the review of the interim efficacy analysis (see Section 9.8.4 for further details).

The primary analysis was conducted, per CSP, from a data extraction performed on 19 March 2021, based on a data cut-off date of 05 March 2021. A total of 190 adjudicated

events met the primary endpoint definition. This analysis was consistent with the CSP and SAP, as agreed upon by the FDA. The high-level results from the primary analysis were shared with the DSMB and included in a corporate press release on 25 March 2021. Approximately 14 potential events meeting the primary endpoint criteria that occurred prior to the data cut-off date had not yet completed the adjudication process. Therefore, an updated data extraction was performed on 29 April 2021, based on the same data cut-off date of 05 March 2021, to ensure that all potential events had completed adjudication, all pending laboratory results were available, and any data cleaning that occurred between 19 March 2021 and 29 April 2021 could be incorporated into an updated analysis. The conclusion on the efficacy for the primary efficacy analysis 76.0% (95% CI: 67.6, 82.2; Falsey 2021b) and interim analysis 78.9% (95% CI: 69.4, 85.4; Appendix 16.1.9) was consistent with the updated primary efficacy analysis, which had a VE estimate of 74.0% (95% CI: 65.34, 80.47; Table 20). This report, therefore, presents the results from the updated primary efficacy analysis, and henceforth, referred to as primary efficacy analysis, in this report.

See Table 14.2.1.1.5.2 for a summary of the criteria for definitions of efficacy endpoints (see Section 8 for study objectives and endpoints).

The results from the analyses of the primary efficacy endpoint are provided in Section 11.1.1, secondary efficacy endpoints are provided in Section 11.1.2, and exploratory efficacy endpoints are provided in Section 11.1.3.

Duration of Follow up

Regardless of unblinding events, the median durations of follow up in the FAS from the second dose in the AZD1222 group was 61 days (range, 1 to 129 days); median duration of follow up from the first dose was 92 days (range, 1 to 190 days) (Table 19). For the placebo group, the median duration of follow up was identical (61 days) from the second dose and similar (91 days) from the first dose. Similar or slightly higher median durations of follow up were observed when duration of follow up was also evaluated by age group (18 to < 65 years and ≥ 65 years) (Table 19). A summary of the duration of follow up for the FVS by age group is also provided (see Table 14.2.1.4.2.2).

The median durations of follow up censored at unblinding events (at the date of unblinding/licensed COVID-19 vaccine administration) in the FAS from the first and second doses of AZD1222 were 80 days (range, 1 to 190 days) and 52 days (range, 1 to 129 days), respectively (see Table 14.2.1.4.1.1).

Table 19 Summary of Duration of Follow Up Time Overall and by Age Group (Full Analysis Set)

Category	Statistic	Overall FAS		18 to < 65 years		≥ 65 years	
		AZD1222 N=21583	Placebo N=10796	AZD1222	Placebo	AZD1222	Placebo
Duration of follow up from first dose (days)	n	21583	10796	16757	8384	4826	2412
	Mean (SD)	93.5 (24.39)	92.7 (25.19)	93.7 (24.48)	92.9 (25.16)	92.8 (24.06)	91.7 (25.25)
	Median	92.0	91.0	92.0	91.0	93.0	92.0
	Min, max	1, 190	1, 189	1, 190	1, 189	8, 188	1, 188
Duration of follow up from second dose (days)	n	20769	9951	16107	7763	4662	2188
	Mean (SD)	64.8 (21.42)	64.9 (21.72)	65.0 (21.26)	64.7 (21.68)	64.4 (21.96)	65.4 (21.83)
	Median	61.0	61.0	61.0	61.0	65.0	66.0
	Min, max	1, 129	1, 129	1, 129	1, 129	1, 129	1, 129

COVID-19 = coronavirus disease-2019; FAS = full analysis set; max = maximum; min = minimum; SD = standard deviation.
Sources: Table 14.2.1.4.1.1 and Table 14.2.1.4.1.2

11.1.1 Primary Efficacy Endpoint

A binary response, whereby a participant with negative serostatus at baseline is defined as a COVID-19 case if their first case of SARS CoV-2 RT PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID 19 case (see Section 9.7).

The results from the analyses of the primary endpoint are provided in Section 11.1.1.1 for primary analysis, Section 11.1.1.2 for sensitivity analyses, Section 11.1.1.3 for supplementary analyses, and Section 11.1.1.4 for subgroup analyses. Additional outputs related to the primary endpoint are provided in Section 11.1.1.5.

Summary tables and figures pertaining to this section are presented in Section 14.2 (Table 14.2.1.1 to Table 14.2.1.1.5.3, and Figure 14.2.1.1.3.1 to Figure 14.2.1.1.4.3) and Appendix 16.2.6.

For potential issues affecting the efficacy evaluation, refer to Section 11.7.1.

11.1.1.1 Primary Analysis of Primary Efficacy Endpoint

The FVS included all participants in the FAS who were seronegative at baseline, received 2 doses of study intervention, and who remained on-study 15 days after their second dose without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. For an overall summary for events occurring ≥ 15 days post second dose of study intervention, see Table 14.2.1.1.

The primary endpoint is a binary response. Statistical significance was achieved if the nominal 95% CI for VE estimate was > 30%. The success criterion for the study was statistically significant with an observed VE point estimate of at least 50%.

The primary efficacy analysis (data cut-off date of 05 March 2021) was based on 203 adjudicated cases. Out of the 203 participants with an event meeting the criteria for the primary endpoint, 10 cases had discordance between central and local RT-PCR results on the same day of collection (see Listing 309.2). Eight of the cases with discordant results satisfied the RT-PCR-positive definition for analysis by having either 1) local negative test and central positive test (6 cases), or 2) local positive test, central negative test, and saliva positive test (2 cases). Another 2 cases did not meet the SAP definition of RT-PCR positive but were adjudicated as having met the primary endpoint definition of a confirmed COVID-19 case, and therefore included in the updated primary efficacy analysis.

- The first case in the AZD1222 group failed to meet the RT-PCR-positive definition because this case had a positive local test and negative central and saliva tests. However, this participant was adjudicated to have met the primary, CDC, and University of Oxford definitions, and adjudication noted the participant had ‘multiple symptoms.’ Moderate or

severe symptoms included severe cough and headache, and moderate body aches, congestion, fatigue, and sore throat. Re-adjudication of this case was performed, and the event was confirmed by the adjudication committee to have met the primary endpoint definition.

- The second case, also in the AZD1222 group, failed to meet the RT-PCR-positive definition because this case had a positive local test and a negative central test, with no saliva test result available. This participant was also adjudicated to have met the primary, CDC, and University of Oxford definitions. The available moderate symptoms in the dataset included congestion and sore throat. Re-adjudication of this case was also performed, and the event was confirmed by the adjudication committee to have met the primary endpoint definition.

For the primary endpoint, in the FVS, there were 73 COVID-19 cases in the AZD1222 group and 130 COVID-19 cases in the placebo group, with a VE estimate of 74.0%, a lower bound of the 95.0% CI of 65.34%, and a 2-sided nominal p-value of < 0.001 for testing the null hypothesis (H0): VE = 30%, which met the pre-specified success criterion (Table 20). In addition, the incidence rate for the AZD1222 group was approximately 4-fold lower than for the placebo group (35.69 cases/1000 person-years vs 137.23 cases/1000 person-years, respectively). In participants ≥ 18 to < 65 years of age, there were 68 COVID-19 cases in the AZD1222 group and 116 COVID-19 cases in the placebo group, with a VE estimate of 72.8% and a lower bound of the 95% CI of 63.35%. In participants ≥ 65 years of age in the FVS, there were 5 COVID-19 cases in the AZD1222 group and 14 COVID-19 cases in the placebo group, with a VE estimate of 83.5% and a lower bound of the 95% CI of 54.17%.

Table 20 First SARS-CoV-2 RT-PCR-positive Symptomatic Illness (Fully Vaccinated Analysis Set)

	AZD1222	Placebo	Vaccine efficacy (%)	(95% CI)	p-value	Met success criteria [a]
Primary analysis						
All participants [b]						
n/N (%)	73/17662 (0.4)	130/8550 (1.5)	73.98	(65.34, 80.47)	< 0.001	Yes
Total follow-up time (1000 person-years)	2.05	0.95	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	35.69	137.23	NA	NA	NA	NA
≥ 18 to < 65 years [c]						
n/N (%)	68/13966 (0.5)	116/6738 (1.7)	72.83	(63.35, 79.87)	NE	Yes
Total follow-up time (1000 person-years)	1.68	0.78	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	40.47	148.99	NA	NA	NA	NA
≥ 65 years [c]						
n/N (%)	5/3696 (0.1)	14/1812 (0.8)	83.50	(54.17, 94.06)	NE	Yes
Total follow-up time (1000 person-years)	0.37	0.17	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	13.69	82.98	NA	NA	NA	NA

[a] The efficacy objective for the primary endpoint was met if the lower bound of the CI for the VE was > 30% and the point estimate for VE was ≥ 50%.

[b] Vaccine efficacy of AZD1222 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study arm as a factor, stratification factor [age group at informed consent] as covariate, as well as the log of the follow up time as an offset). The p-value for the primary endpoint was VE versus 30%.

[c] Vaccine efficacy of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance (including study arm as well as the log of the follow up time as an offset) for each age group.

Note: Vaccine efficacy was defined as 1 - (incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio was from the Poisson regression model. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio from the model.

Note: The observation period for the endpoint was 15 days post second dose up to data cut-off date, or up to the date of the intercurrent event. An intercurrent event was defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and was treated as no event. Total follow-up time was the sum of the observation periods over all participants in the subgroup in the study arm divided by 1000.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: Coronavirus disease-2019 endpoints were based on adjudicated events.

CI = confidence interval; COVID-19 = coronavirus disease-2019; NA = not applicable; NE = not evaluable; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Tables 14.2.1.1.1 and 14.2.1.1.4.1.

11.1.1.2 Sensitivity Analyses of Primary Efficacy Endpoint

Two planned sensitivity analyses were conducted and evaluated the following 2 different approaches for imputation of missing data and are summarized in Table 21:

- Multiple imputation assuming the observed event rate per study arm
- Multiple imputation assuming the observed placebo event rate for both arms

When the observed event rate from the randomized study arm was applied, the VE estimate was consistent with the primary efficacy analysis (73.3%) with a lower bound of the 95.0% CI of 64.59%, and a 2-sided p-value of < 0.001 for testing H0: VE = 30%.

When the higher observed placebo event rate was applied to both study intervention arms, the VE estimate approached the primary efficacy analysis (65.3%) with a lower bound of the 95.0% CI of 53.37%, and a 2-sided p-value of < 0.001 for testing H0: VE = 30%.

Table 21 Sensitivity Analyses for Vaccine Efficacy for Imputed Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Analysis Set)

	AZD1222 N=17662	Placebo N=8550	Vaccine efficacy (%)	95% CI	p-value	Met success criteria [a]
FVS – Imputation using observed event rate per study arm [b]						
n (%), observed events	73 (0.4)	130 (1.5)	see below	see below	see below	see below
n (%), no events	11346 (64.2)	5071 (59.3)	NA	NA	NA	NA
n (%), participants requiring imputation [c]	6243 (35.3)	3349 (39.2)	NA	NA	NA	NA
Mean total events from 20 imputed datasets	81.4 (0.5)	147.2 (1.7)	73.29	64.59, 79.85	< 0.001	Yes
FVS – Imputation assuming the observed placebo event rate to both arms [c]						
n (%), observed events	73 (0.4)	130 (1.5)	see below	see below	see below	see below
n (%), no events	11346 (64.2)	5071 (59.3)	NA	NA	NA	NA
n (%), participants requiring imputation [c]	6243 (35.3)	3349 (39.2)	NA	NA	NA	NA
Mean total events from 20 imputed datasets	105.9 (0.6)	147.2 (1.7)	65.30	53.37, 74.18	< 0.001	Yes

[a] The efficacy objective for the primary endpoint was met if the lower bound of the CI for the VE was > 30% and the point estimate for VE was ≥ 50%.

[b] Twenty imputed datasets were generated where the missing values were imputed using the observed event rate per study arm conditional on age group at informed consent.

[c] Twenty imputed datasets were generated where the missing values were imputed using the observed placebo event rate conditional on age group at informed consent.

[d] Participants who had no events and withdrew from the study prior to the time of analysis or were unblinded to study intervention/received authorized COVID-19 vaccine prior to having met the criteria for the efficacy endpoint.

Note: The VE of AZD1222 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study arm as a factor and stratification factor [age group at inform consent]). Results from the analysis of each imputed dataset were combined using Little and Rubin's imputation rules.

Note: The VE was defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio was from the Poisson regression model. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio from the model.

Note: The observation period for the endpoint was 15 days post second dose up data cut-off date, or up to the date of the intercurrent event.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: COVID-19 endpoints were based on adjudicated events.

Note: Mean total events included both observed events and additional events imputed for participants with censored follow-up time through to the data cut-off date.

CI = confidence interval; COVID-19 = coronavirus disease-2019; FVS = fully vaccinated analysis set; NA=not applicable; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Table 14.2.1.1.2.1 and Table 14.2.1.1.2.2

11.1.1.3 Supplementary Analyses of Primary Efficacy Endpoint

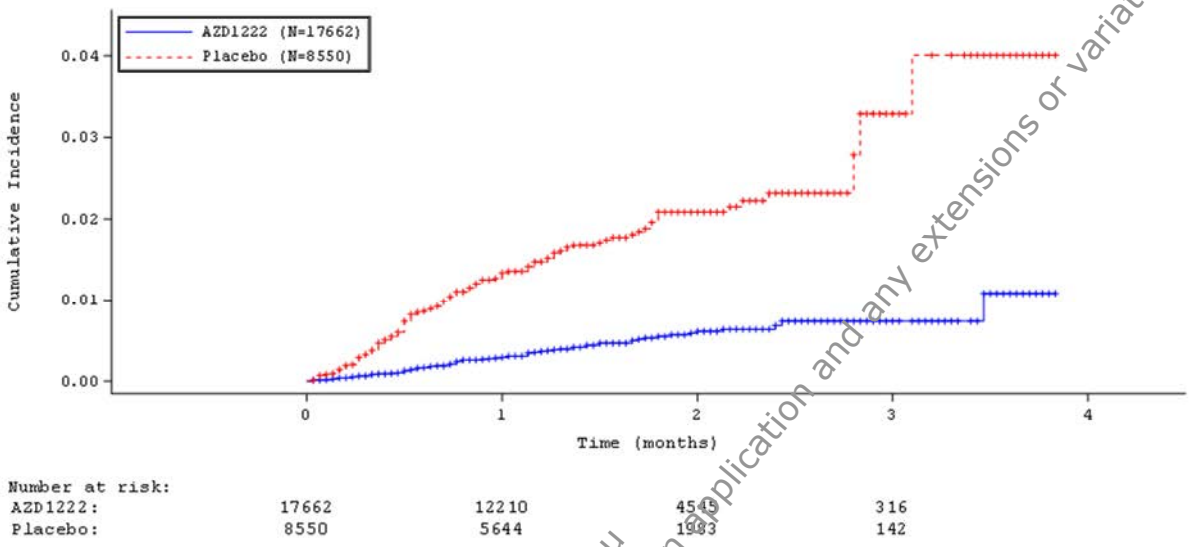
The following 4 supplementary analyses of the primary endpoint were planned analyses in the SAP and are discussed below:

- A Cox Proportional Hazards model was used to determine time to first case of SARS-CoV-2 RT-PCR positive symptomatic COVID-19 occurring ≥ 15 days post second dose of study intervention
- Primary efficacy analysis using the PPS
- Primary efficacy analysis excluding participants whose second dose was out of window due to clinical hold (ie, participants who received their first dose of study intervention between 28 August 2020 and 06 September 2020)
- Primary efficacy analysis including the entire follow-up time, regardless of unblinding to treatment assignment or receipt of authorized COVID-19 vaccine

Time to Event Using Cox Proportional Hazard Model

A cumulative incidence curve of the time to first case of SARS-CoV-2 RT-PCR positive symptomatic COVID-19 occurring ≥ 15 days post second dose of study intervention is presented in Figure 4, showing clear early separation of the curve for the AZD1222 group from the placebo group at 15 days post second dose that continues to diverge over time.

Figure 4 **Cumulative Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention - Supplementary Analysis #1 (Fully Vaccinated Analysis Set)**



Note: The time to first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, in days, was calculated as follows: Date of SARS-CoV-2 RT-PCR-positive test – (date of second dose of study intervention + 14) + 1. For censored participants, the censoring time was from (date of second dose of study intervention + 14) to last observed time during the analysis period/unblinding/authorized COVID-19 vaccine administration.

Note: COVID-19 endpoints were based on adjudicated events.

COVID-19 = coronavirus disease-2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

Source: Figure 14.2.1.1.3.1

Using the Cox Proportional Hazard model, the supplementary analysis of the time to primary endpoint further demonstrated similar results to those observed for the primary efficacy analysis with a VE estimate of 73.9% (95% CI: 65.34%, 80.48%) (Table 22).

Table 22 Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Cox Proportional Hazard Model (Fully Vaccinated Analysis Set)

	AZD1222 N=17662	Placebo N=8550
Number of participants with events, n (%)	73 (0.4)	130 (1.5)
Number of participants censored, n (%)	17589 (99.6)	8420 (98.5)
Reason for censoring, n (%)		
Study discontinuation prior to having an event	143 (0.8)	96 (1.1)
No event	11346 (64.2)	5071 (59.3)
Participant unblinded/received authorized COVID-19 vaccine	6100 (34.5)	3253 (38.0)
Kaplan Meier product-limit estimates		
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, max	1, 115*	1, 115*
Percent of participants without events (95% CI) [no. at risk] Timing relative to 15 days after second dose		
Month 1 (Day 30)	99.7 (99.6, 99.8) (n=12210)	98.7 (98.4, 98.9) (n=5644)
Month 2 (Day 60)	99.4 (99.2, 99.5) (n=4545)	97.9 (97.5, 98.3) (n=1983)
Month 3 (Day 90)	99.3 (99.0, 99.4) (n=316)	96.7 (94.9, 97.9) (n=142)
Vaccine efficacy (%)	73.89	NA
95% CI	(65.34, 80.48)	NA

Note: The time to first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, in days, was calculated as follows: Date of SARS-CoV-2 RT-PCR-positive test - (date of second dose of study intervention +14) +1. For censored participants, the censoring time was from (date of second dose of study intervention + 14) to last observed time during the analysis period/unblinding/authorized COVID-19 vaccine administration.

Note: Time to event was fit using the PH model with study arm as a factor and age group at informed consent as covariate.

Note: The VE was 1-(hazard rate for AZD1222 arm / hazard rate for placebo arm), where the hazard ratio was from the PH model with Efron method. The 95% CI for the VE was obtained by taking 1 minus the 95 %profile likelihood CI of the hazard ratio from the PH model.

Note: Percentages were based on the number of participants in the analysis set by study arm and COVID-19 endpoints were based on adjudicated events.

* Indicates a censored observation.

CI = confidence interval; COVID-19 = coronavirus disease-2019; NA = not applicable; NE = not evaluable; no. = number; PH = Cox Proportional Hazard; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

Source: Table 14.2.1.1.3.1

Vaccine Efficacy of the Primary Efficacy Endpoints with Changes to Participant Inclusion

The following 3 supplementary analyses of the primary endpoint are summarized in Table 23 and demonstrate that the efficacy results are robust, and the VE estimates were highly consistent with the primary efficacy analysis (range: 73.4% to 74.3%):

- Primary efficacy analysis using the PPS
- Primary efficacy analysis excluding participants whose second dose was out of window due to clinical hold (see Section 7.4 for details on clinical hold)
- Primary efficacy analysis including the entire follow-up time, regardless of unblinding to treatment assignment or receipt of authorized COVID-19 vaccine.

Of particular interest, the primary efficacy analysis conducted excluding the participants whose second dose was out of window due to clinical hold gave consistent results with the primary efficacy analysis (VE estimate [95% CI] of 73.4% [63.84, 80.37]) (Table 23), suggesting that the delay in second dose did not have a clinically meaningful impact on VE estimate.

Table 23 Supplementary Analyses of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated or Per-protocol Analysis Sets)

	AZD1222	Placebo	Vaccine efficacy (%)	95% CI	p-value
Per-protocol analysis set					
n/N (%)	72/17534 (0.4)	129/8337 (1.5)	74.23	65.61, 80.69	< 0.001
Total follow-up time (1000 person-years)	2.04	0.94	NA	NA	NA
Incidence rate (cases per 1000 person-years)	35.35	137.25	NA	NA	NA
FVS excluding participants with out-of-window dose 2 due to clinical hold					
n/N (%)	65/17160 (0.4)	113/8301 (1.4)	73.36	63.84, 80.37	< 0.001
Total follow-up time (1000 person-years)	1.92	0.89	NA	NA	NA
Incidence rate (cases per 1000 person-years)	33.77	126.84	NA	NA	NA
FVS regardless of unblinding					
n/N (%)	76/17662 (0.4)	140/8550 (1.6)	74.32	66.04, 80.58	< 0.001
Total follow-up time (1000 person-years)	2.52	1.20	NA	NA	NA
Incidence rate (cases per 1000 person-years)	30.11	116.96	NA	NA	NA

Note: The VE of AZD1222 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study arm as a factor, stratification factor [age group at inform consent] as covariate as well as the log of the follow-up time as an offset).

Note: The VE was defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio was from the Poisson regression model. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio from the model.

Note: The observation period for the endpoint was 15 days post second dose up to data cut-off date, or up to the date of the intercurrent event. An intercurrent event was defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and is treated as no event. Total follow-up time is the sum of the observation periods over all participants in the study arm divided by 1000.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: COVID-19 endpoints were based on adjudicated events.

Note: Participants affected by the clinical hold are those who received their first dose of study intervention between 28 August 2020 and 06 September 2020.

CI = confidence interval; COVID-19 = coronavirus disease-2019; FVS = fully vaccinated analysis set; NA = not applicable; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Table 14.2.1.1.3.2, Table 14.2.1.1.3.3, Table 14.2.1.1.3.4, Table 14.2.1.1.3.5

11.1.1.4 Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses of the primary efficacy endpoint were performed to provide additional information on the applicability of these results across the general population.

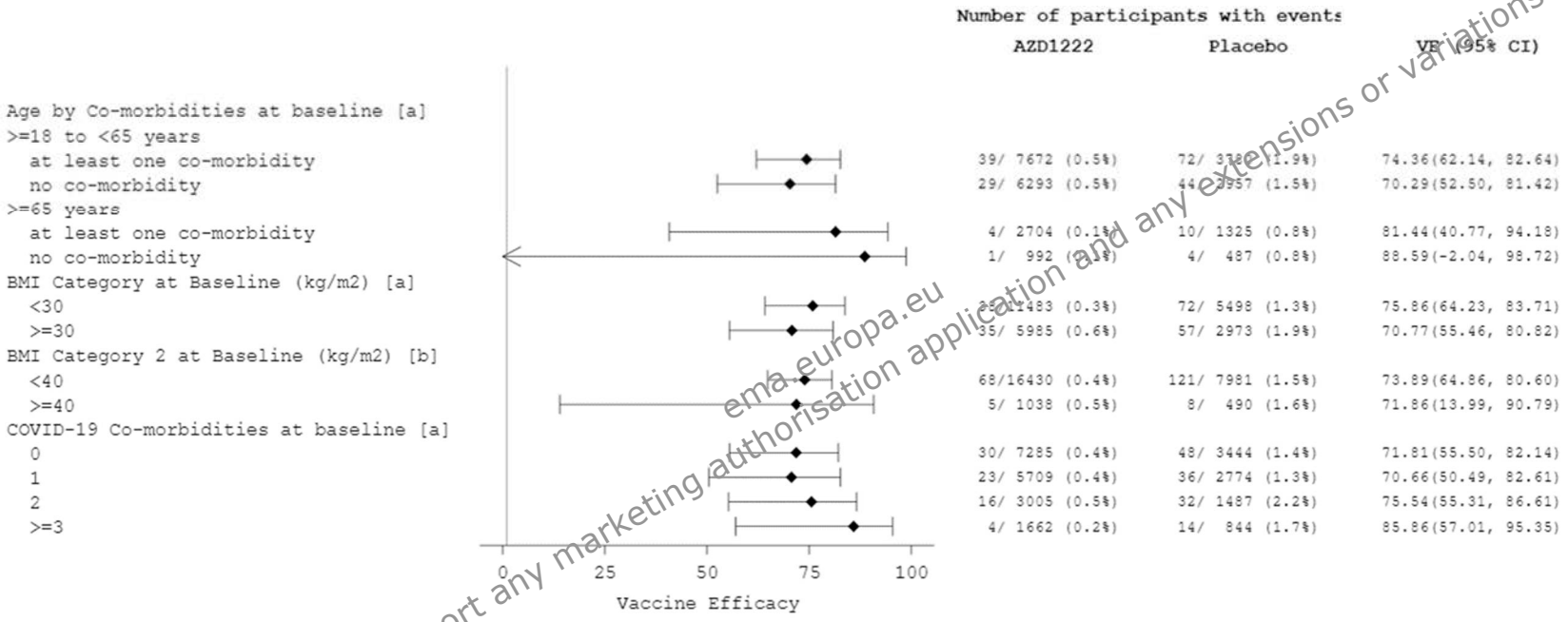
Subgroup analyses for the primary efficacy endpoint included determination of VE estimates based on age, sex, race, ethnicity, country, BMI, comorbidity risk factor, baseline SARS-CoV-2 status, and individual comorbidity risk factors, and results are shown graphically in Figure 5, Figure 6, and Figure 7. See Section 10.4 for a list of comorbidities included in the analysis. Additional information regarding follow-up time and incidence rates for each study intervention arm are also provided (see Tables 14.2.1.1.4.1 through 14.2.1.1.4.12, inclusive).

In general, VE estimates among the subgroups was similar to the VE estimate seen in the overall study population. Robust efficacy was observed regardless of age, gender, and ethnicity. Caution in interpretation is warranted for the individual VE estimate results of certain subgroups with small number of cases, such as race for American Indians or Alaska Native or country for Chile and Peru. Even with the low event numbers, a beneficial trend for the VE estimate for these subgroup categories was still directionally favorable for AZD1222. It should be noted that the results for baseline seronegative participants (VE 72.9%, 95% CI: 63.59, 79.92) do not match the primary analysis results (VE 74.0%, 95% CI: 65.34, 80.47), as a different model was used for the serostatus at baseline subgroup (stratified Poisson regression with exact conditional method versus Poisson regression with robust variance). Stratified Poisson regression with exact conditional method was used for serostatus at baseline subgroup because there were no participants in the AZD1222 group and 1 participant in the placebo group with baseline seropositive status; therefore, the Poisson regression with robust variance did not converge.

With respect to comorbidities, the VE estimates were similar to the overall population for participants with 1, 2 or ≥ 3 comorbidities, and no differences were observed among the comorbidity by age category subgroups (Figure 5). In the ≥ 65 group, despite presence of pre-defined comorbidities, vaccine efficacy was consistent (Figure 5 and Figure 6). Determination of VE estimate was conducted for each individual pre-defined comorbidity of risk and is provided (Figure 7).

For potential issues affecting the efficacy evaluation, refer to Section 11.7.1.

Figure 5 Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression Model by Subgroup (Fully Vaccinated Analysis Set)



[a] The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance (including study arm, age group at informed consent as well as the log of the follow-up time as an offset) for each level of the subgroup. For subgroups corresponding to one of the factor levels included in the analysis model, the corresponding factor was not included in the model.

[b] The VE of AZD1222 versus placebo and the 95% CI were estimated based on reduced Poisson regression model (including study arm as well as the log of the follow-up time as an offset).

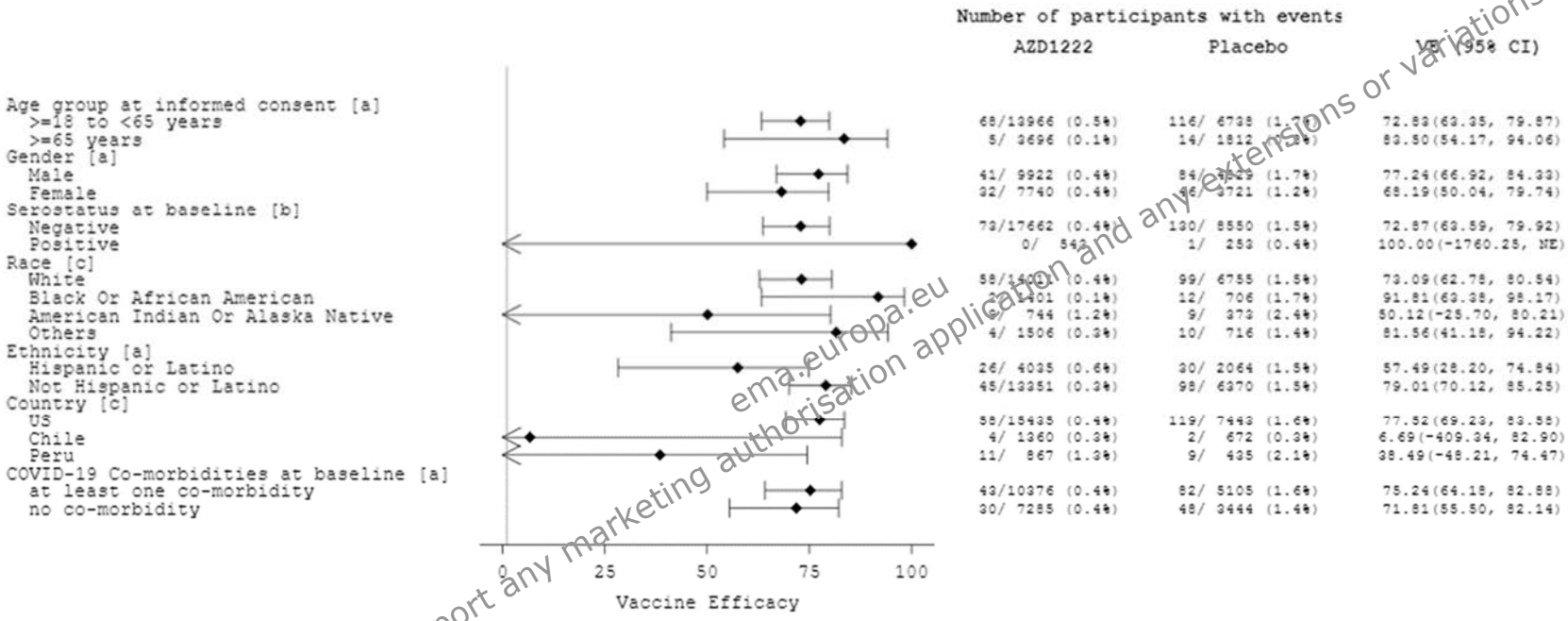
Note: COVID-19 endpoints were based on adjudicated events.

Note: Arrows at the extremity of the CI indicate truncated values. Refer to "95% CI" column for actual values.

BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease-2019; FVS = fully vaccinated analysis set; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Figure 14.2.1.1.4.2

Figure 6 **Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression Model by Subgroup - Continued (Fully Vaccinated Set)**



[a] The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance (including study arm, age group at informed consent as well as the log of the follow-up time as an offset) for each level of the subgroup. For subgroups corresponding to one of the factor levels included in the analysis model, the corresponding factor was not included in the model.

[b] The VE of AZD1222 versus placebo and the exact 95% or 1-sided 97.5% CI were estimated based on stratified Poisson regression with exact conditional method (including study arm as factor, stratification factor [age group at informed consent] as strata factor as well as the log of total number of participants for each combination of study arm and strata as an offset).

[c] The VE of AZD1222 versus placebo and the 95% CI were estimated based on reduced Poisson regression model (including study arm as well as the log of the follow-up time as an offset).

Note: Analysis for subgroup of serostatus included participants in the fully vaccinated analysis set regardless of baseline serostatus.

Note: Asian, Native Hawaiian or Other Pacific Islander, multiple, unknown and not reported races are included in the category of Others.

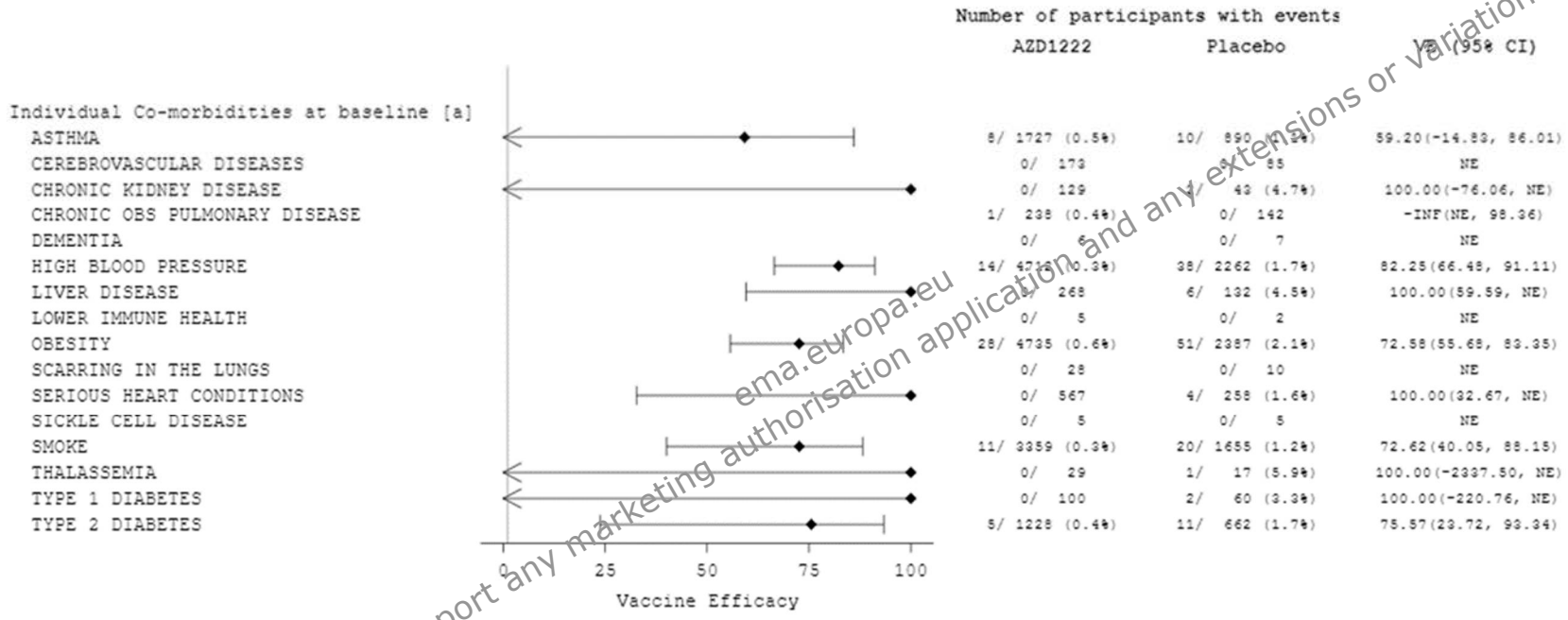
Note: Arrows at the extremity of the CI indicate truncated values. Refer to "95% CI" column for actual values.

Note: COVID-19 endpoints were based on adjudicated events.

CI = confidence interval; COVID-19 = coronavirus disease-2019; FVS = fully vaccinated analysis set; NE = not evaluable; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; US = United States; VE = vaccine efficacy.

Source: Figure 14.2.1.1.4.1

Figure 7 **Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression Model by Pre-defined COVID-19 Comorbidity Supplemental Subgroup (Fully Vaccinated Set)**



[a] The VE of AZD1222 versus control and the exact 95% or 1-sided 97.5% CI were estimated based on stratified Poisson regression with exact conditional method (including study arm as factor, stratification factor [age group at informed consent] as strata factor as well as the log of total number of participants for each combination of study arm and strata as an offset) for each level of the subgroup.

Note: Arrows at the extremity of the CI indicate truncated values. Refer to "95% CI" column for actual values.

Note: COVID-19 endpoints were based on adjudicated events.

CI = confidence interval; COVID-19 = coronavirus disease-2019; FVS = fully vaccinated analysis set; INF = infinity; NE = not evaluable; OBS = obstructive; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Figure 14.2.1.1.4.3

11.1.1.5 Additional Outputs Supporting the Primary Efficacy Endpoint

Table 24 provides a list of additional analyses related to the supplementary and subgroups analyses of the primary endpoint. Refer to Section 14.2 for these outputs.

Table 24 Additional Summary Tables supporting the Supplementary and Subgroup Evaluations of the Primary Efficacy Endpoint

Table number	Title
Other supplementary analyses	
Table 14.2.1.1.3.2	Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression with Robust Variance by Time Interval of Illness Onset - Supplementary Analysis #2 (FVS)
Table 14.2.1.1.3.3	Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression with Robust Variance - Supplementary Analyses #3 (PP Analysis Set)
Related to subgroup analyses	
Table 14.2.1.1.1.1	Overall Efficacy Summary for Events Occurring ≥ 15 Days Post Second Dose of Study Intervention by baseline serostatus
Table 14.2.1.1.1.2	Overall Efficacy Summary for Events Occurring ≥ 15 Days Post Second Dose of Study Intervention by age group at informed consent
Table 14.2.1.1.1.3	Overall Efficacy Summary for Events Occurring ≥ 15 Days Post Second Dose of Study Intervention by sex
Table 14.2.1.1.1.4	Overall Efficacy Summary for Events Occurring ≥ 15 Days Post Second Dose of Study Intervention by race
Table 14.2.1.1.1.5	Overall Efficacy Summary for Events Occurring ≥ 15 Days Post Second Dose of Study Intervention by COVID-19 comorbidities at baseline
Table 14.2.1.1.1.6	Overall Efficacy Summary for Events Occurring ≥ 15 Days Post Second Dose of Study Intervention by age group at informed consent and comorbidities at baseline

11.1.2 Secondary Efficacy Endpoints

Summary tables and figures pertaining to this section are presented in Section 14.2 (Table 14.2.1.2.1.1 to Table 14.2.1.2.7.3, and Figure 14.2.1.2.2.2 to Figure 14.2.1.3.5.1) and Appendix 16.2.6.

For an overview of number of participants with SARS CoV-2 RT-PCR-positive symptomatic illnesses occurring ≥ 15 days post second dose for the FVS, see Table 14.2.1.1.5.1.1. For an overview of number of participants with SARS-CoV-2-RT-PCR-positive symptomatic illnesses occurring post first dose for the FAS, see Table 14.2.1.1.5.1.2.

For potential issues affecting the efficacy evaluation, refer to Section 11.7.1.

11.1.2.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are the incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study

intervention regardless of evidence of prior SARS-CoV-2 infection; the incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention; the incidence of COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention; and the incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention.

All 4 key secondary endpoints were statistically significant using the hierarchical fixed sequence testing method, such that each of the 2-sided 95% CIs for the VE estimates were > 0% (see Section 7.4 of the SAP) (Table 25). The numerical order of the hierarchical testing is noted below.

Key Secondary Efficacy Endpoint 1

For the key secondary endpoint 1 of first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurring ≥ 15 days post second dose regardless of evidence of prior SARS-CoV-2 infection, there were 76 COVID-19 cases in the AZD1222 group and 135 COVID-19 cases in the placebo group, with a VE of 73.7%, a lower bound of the 95% CI of 65.13%, and a 2-sided p-value of < 0.001 for testing H0: VE = 0%.

Key Secondary Efficacy Endpoint 2

For the key secondary endpoint 2 of the incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose, there were no COVID-19 cases in the AZD1222 group and 8 COVID-19 cases in the placebo group, with a VE estimate of 100.0%, a lower bound of the 1-sided 97.5% CI of 71.62%, and a corresponding p-value of < 0.001 for testing H0: VE = 0%. Per the US FDA Guidance for Industry Development and Licensure of Vaccines to Prevent COVID-19 (FDA 2020), a minimum of 5 severe cases in the placebo group is considered sufficient to assess the benefit:risk for vaccine-enhanced respiratory disease. Given the observation of 8 severe COVID-19 cases in the placebo group and none in the AZD1222 group, this vaccine does not appear to induce such enhanced respiratory disease.

Key Secondary Efficacy Endpoint 3

For the key secondary endpoint 3 of the incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose, there was one COVID-19 case in the AZD1222 group and 9 COVID-19 cases in the placebo group, with a VE estimate of 94.8%, a lower bound of the 95% CI of 58.98%, and a 2-sided p-value of 0.005 for testing H0: VE = 0%. Of the 8 participants in the placebo group who had severe or critical cases, all had emergency department visits.

Key Secondary Efficacy Endpoint 4

For the key secondary endpoint 4 of the incidence of the first post-treatment response for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention, there were 156 COVID-19 cases in the AZD1222 group and 202 COVID-19 cases in the placebo group, with a VE estimate of 64.3%, a lower bound of the 95% CI of 56.05%, and a 2-sided p-value of < 0.001 for testing H0: VE = 0%.

Table 25 Summary of Efficacy Analysis Results for Key Secondary Efficacy Endpoints ≥ 15 days (Fully Vaccinated Set)

Endpoint	AZD1222	Placebo	Vaccine efficacy (%)	(95 % CI)	p-value	Met success criteria [a]
Key secondary endpoints						
Symptomatic COVID-19 regardless of evidence of prior SARS-CoV-2 infection [b]						
n/N (%)	76/18563 (0.4)	135/9031 (1.5)	73.68	(65.13, 80.13)	< 0.001	Yes
Total follow-up time (1000 person-years)	2.15	1.01	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	35.34	134.27	NA	NA	NA	NA
COVID-19 severe or critical symptomatic illness [c]						
n/N (%)	0/17662 (0)	8/8550 (< 0.1)	100.00	(71.62 [d] NE)	< 0.001	Yes
Total follow-up time (1000 person-years)	2.05	0.95	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	0	8.44	NA	NA	NA	NA
COVID-19-related emergency department visits [b]						
n/N (%)	1/17662 (< 0.1)	9/8550 (0.1)	94.80	(58.98, 99.34)	0.005	Yes
Total follow-up time (1000 person-years)	2.05	0.96	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	0.49	9.36	NA	NA	NA	NA
Post-treatment response for SARS-CoV-2 Nucleocapsid antibodies [b, e]						
n/N (%)	156/17662 (0.9)	202/8550 (2.4)	64.32	(56.05, 71.03)	< 0.001	Yes
Total follow-up time (1000 person-years)	2.03	0.94	NA	NA	NA	NA
Incidence rate (cases per 1000 person-years)	76.86	215.37	NA	NA	NA	NA

[a] The 4 key secondary endpoints were evaluated at a 5% nominal significance level using hierarchical fixed-sequence testing in the order above. If the 2-sided 95% CI was >0%, statistical significance was achieved, and the next key secondary endpoint was evaluated.

[b] The VE of AZD1222 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study arm as a factor, stratification factor [age group at inform consent] as covariate as well as the log of the follow-up time as an offset). VE is defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio is from the Poisson regression model. The 95% CI for the VE is obtained by taking 1 minus the 95% CI of the risk ratio from the model. The observation period for the endpoint was 15 days post second dose up to data cut-off date, or up to the date of the intercurrent event. An intercurrent event is defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and is treated as no event. Total follow-up time is the sum of the observation periods over all participants in the study arm divided by 1000. Percentages are based on the number of participants in the analysis set by study arm. COVID-19 endpoints are based on adjudicated events.

[c] The VE of AZD1222 versus placebo, the exact 1-sided 97.5% CI and p-value were estimated based on stratified Poisson regression with exact conditional method (including study arm as factor, stratification factor [age group at informed consent] as strata factor as well as the log of total number of participants for each combination of study arm and strata as an offset). VE is defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio is from the stratified Poisson regression with exact conditional method. The 1-sided 97.5% CI for the VE is obtained by taking 1 minus the 1-sided 97.5% CI of the risk ratio derived from the model. The observation period for the endpoint was 15 days post second dose up to data cut-off date, or up to the date of the of intercurrent event. An intercurrent event is defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and is treated as no event. Total follow-up time is the sum of the observation periods over all participants in the study arm divided by 1000.

[d] One-sided 97.5% CI.

[e] Negative at baseline to positive post treatment with study intervention.

Note: COVID-19 endpoints were based on adjudicated events.

CI = confidence interval; COVID-19 = coronavirus disease-2019; n = number of participants meeting endpoint criteria, percentages are based on number of participants in the analysis set by study arm; NA = not applicable; NE = not evaluable; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Tables 14.2.1.2.4.1, 14.2.1.2.5.1, 14.2.1.2.7.1 and 14.2.1.2.1.3

Additional Outputs Supporting the Key Secondary Efficacy Endpoints

Table 26 provides a list of additional analyses related to the key secondary efficacy endpoints. Refer to Section 14.2 for these outputs.

Table 26 Additional Summary Tables Supporting the Key Secondary Efficacy Endpoints

Table number	Title
Key Secondary Efficacy Endpoint 1	
Table 14.2.1.2.4.2	Time to First SARS-CoV-2 RT-PCR Positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Regardless of Evidence of Prior SARS-CoV-2 Infection (FVS Regardless of Baseline Serostatus)
Figure 14.2.1.2.4.2	Cumulative Incidence of First SARS-CoV-2 RT-PCR Positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Regardless of Evidence of Prior SARS-CoV-2 Infection (FVS Regardless of Baseline Serostatus)
Key Secondary Efficacy Endpoint 2	
Table 14.2.1.2.5.2	Time to First SARS-CoV-2 RT-PCR-positive Severe or Critical Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention (FVS)
Figure 14.2.1.2.5.2	Cumulative Incidence of First SARS-CoV-2 RT-PCR-positive Severe or Critical Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention (FVS)
Table 14.2.1.2.5.3	Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Severe or Critical Symptomatic COVID-19 Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression with Robust Variance by Serostatus at Baseline (FVS Regardless of Baseline Serostatus)
Key Secondary Efficacy Endpoint 3	
Table 14.2.1.2.7.2	Time to First COVID-19-related Emergency Department Visits Occurring ≥ 15 Days Post Second Dose of Study Intervention (FVS)
Figure 14.2.1.2.7.2	Cumulative Incidence of First COVID-19-related Emergency Department Visits Occurring ≥ 15 Days Post Second Dose of Study Intervention (FVS)
Table 14.2.1.2.7.3	Vaccine Efficacy for Incidence of First COVID-19-related Emergency Department Visits Occurring ≥ 15 Days Post Second Dose of Study Intervention Using Poisson Regression with Robust Variance by Serostatus at Baseline (FVS Regardless of Baseline Serostatus)
Key Secondary Efficacy Endpoint 4	
Table 14.2.1.2.1.1	The Proportion of Participants Who Have a Post-treatment Response for SARS-CoV-2 Nucleocapsid Antibodies Over Time - Secondary Analysis (Full Analysis Set)
Table 14.2.1.2.1.2	The Proportion of Participants Who Have a Post-treatment Response for SARS-CoV-2 Nucleocapsid Antibodies Over Time by PCR Status - Secondary Analysis (Full Analysis Set)

Subgroup analyses of the key secondary efficacy endpoints were performed to provide additional information on the applicability of these results across the general population: by age group (Table 14.2.1.1.1.2), by gender (Table 14.2.1.1.1.3), by race (Table 14.2.1.1.1.4), by comorbidities at baseline (Table 14.2.1.1.1.5), and by age and comorbidities at baseline (Table 14.2.1.1.1.6). Refer to Section 14.2 for these outputs.

11.1.2.2 Efficacy Using CDC or University of Oxford Criteria

Results for the 2 secondary endpoints evaluating VE estimates using either the CDC or University of Oxford criteria are summarized in Table 27. Regardless of the criteria used, strong efficacy that met the success criteria was demonstrated in the AZD1222 group relative to the placebo group.

Time to first event analyses when events were defined by either the CDC or University of Oxford criteria (see Table 14.2.1.2.2.2 and Table 14.2.1.2.3.2, respectively) were conducted and summarized using Kaplan-Meier summary statistics. Similarly, cumulative incidence graphs were generated and show a consistent pattern as the primary efficacy analysis (see Figure 14.2.1.2.2.2 [CDC criteria] and Figure 14.2.1.2.3.2 [Oxford criteria]).

Incidence of the First Case of SARS-CoV-2 RT-PCR Positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using CDC Criteria

For the secondary endpoint of the efficacy of 2 IM doses of AZD1222 compared with placebo for the prevention of symptomatic COVID-19 using CDC criteria, there were 95 COVID-19 cases in the AZD1222 group and 145 COVID-19 cases in the placebo group, with a VE estimate of 69.7%, a lower bound of the 95% CI of 60.68%, and a 2-sided p-value of < 0.001 for testing H0: VE = 0%.

Incidence of the First Case of SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using University of Oxford-defined Symptom Criteria

For the secondary endpoint of the efficacy of 2 IM doses of AZD1222 compared with placebo for the prevention of symptomatic COVID-19 using the University of Oxford criteria, there were 86 COVID-19 cases in the AZD1222 group and 136 COVID-19 cases in the placebo group, with a VE estimate of 70.7%, a lower bound of the 95% CI of 61.62%, and a 2-sided p-value of < 0.001 for testing H0: VE = 0%.

Table 27 Vaccine Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Under Either the CDC Criteria or the University of Oxford Criteria (Fully Vaccinated Set)

Endpoint	AZD1222	Placebo	Vaccine efficacy (%)	(95% CI)	p-value
CDC criteria					
n/N (%)	95/17662 (0.5)	145/8550 (1.7)	69.65	(60.68, 76.57)	< 0.001
Total follow-up time (1000 person-years)	2.05	0.95	NA	NA	NA
Incidence rate (cases per 1000 person-years)	46.45	153.07	NA	NA	NA
University of Oxford criteria					
n/N (%)	86/17662 (0.5)	136/8550 (1.6)	70.70	(61.62, 77.64)	< 0.001
Total follow-up time (1000 person-years)	2.05	0.95	NA	NA	NA
Incidence rate (cases per 1000 person-years)	42.05	143.57	NA	NA	NA

Note: The VE of AZD1222 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study arm as a factor, stratification factor [age group at inform consent] as covariate as well as the log of the follow-up time as an offset).

Note: The VE was defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio is from the Poisson regression model. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio from the model.

Note: The observation period for the endpoint was 15 days post second dose up to data cut-off date, or up to the date of the intercurrent event. An intercurrent event was defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and was treated as no event.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: COVID-19 endpoints were based on adjudicated events.

CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease-2019; FVS = fully vaccinated analysis set; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Tables 14.2.1.2.2.4 and 14.2.1.2.3.1

11.1.2.3 Efficacy Following First Dose

Incidence of SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post First Dose of Study Intervention

Analyses were performed to assess efficacy against COVID-19 after one dose of AZD1222. In participants in the FAS who had an adjudicated SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 case post first dose (regardless of whether the participant received a second dose), the VE estimate for RT-PCR-positive symptomatic illness after one dose was 54.5% (95% CI 46.48, 61.26) (Table 28).

The increased VE estimate over time is also shown with the cumulative incidence of adjudicated SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 case post first dose

(Figure 8) and shows the expected overlap of study intervention arms during the first few weeks when immunity is developing. Time to first SARS-CoV-2 RT-PCR-positive symptomatic illness post first dose was also determined (see Table 14.2.1.3.5.1).

Incidence of SARS-CoV-2 RT-PCR-positive Severe or Critical Symptomatic Illness Occurring Post First Dose of Study Intervention

In participants in the FAS who had an adjudicated SARS-CoV-2 RT-PCR-positive severe or critical COVID-19 illness, the VE estimate for AZD1222 post first dose for such events was 85.0% (95% CI 58.97, 94.50) (Table 28). Of note, this estimate is based on 21 events overall (5 in the AZD1222 group and 16 in the placebo group). Time to first SARS-CoV-2-RT-PCR-positive severe or critical symptomatic COVID-19 occurring post first dose of study intervention is provided for seronegative participants in the FAS (see Table 14.2.1.2.6.2) with cumulative incidence shown graphically (see Figure 14.2.1.2.6.2).

Table 28 First COVID-19 SARS-CoV-2 RT-PCR-positive Illness Occurring Post First Dose of Study Intervention (Full Analysis Set, Seronegative at Baseline)

	AZD1222	Placebo	Vaccine efficacy (%)	95% CI
Symptomatic illness				
Any time after dose 1, n/N (%)	287/20589 (1.4)	303/10300(2.9)	54.47	46.48, 61.26
Total follow-up time (1000 person-years)	4.42	2.12	NA	NA
Incidence rate (cases per 1000 person-years)	64.98	142.69	NA	NA
Severe or critical symptomatic illness				
Any time after dose 1, n/N (%)	5/20589 (< 0.1)	16/10300 (0.2)	84.97	(58.97, 94.50)
Total follow-up time (1000 person-years)	4.42	2.12	NA	NA
Incidence rate (cases per 1000 person-years)	1.13	7.53	NA	NA

Note: The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance (including study arm and age group at screening (18-65 years, ≥ 65 years) as covariates as well as the log of the follow-up time as an offset).

Note: The VE was defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio is from the Poisson regression model. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio from the model.

Note: The observation period for the endpoint was post first dose up to data cut-off date, or up to the date of the intercurrent event. An intercurrent event was defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and was treated as no event.

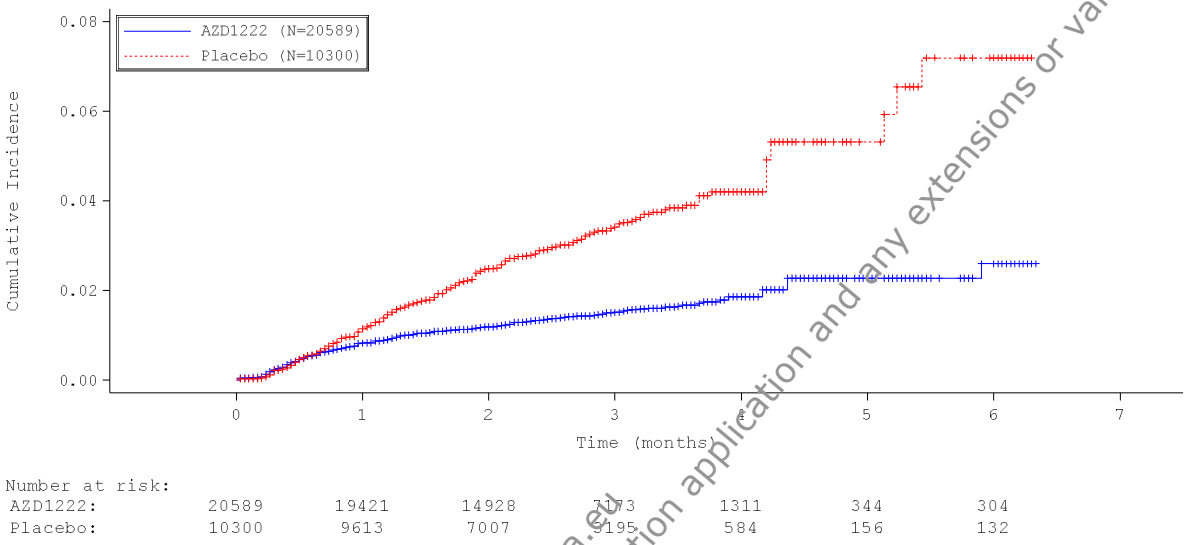
Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: COVID-19 endpoints were based on adjudicated events.

CI = confidence interval; COVID-19 = coronavirus disease-2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Tables 14.2.1.3.5.2 and 14.2.1.2.6.1

Figure 8 **Cumulative Incidence Plot for Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post First Dose of Study Intervention (Full Analysis Set, Seronegative at Baseline)**



Note: The time to COVID-19 SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention, in days, was calculated as follows: Date of first event - Date of first dose of study intervention +1. For censored participants, the censoring time was from date of first dose of study intervention to last observed time during the analysis period/unblinding/authorized COVID-19 vaccine administration.

Note: COVID-19 endpoints were based on adjudicated events.

Note: + Indicates a censored observation.

COVID-19 = coronavirus disease-2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

Source: Figure 14.2.1.3.5.1

11.1.3 Exploratory Efficacy Endpoints

At ≥ 15 days post second dose in the FVS, high VE estimates were demonstrated for hospitalizations (94.2%, which includes ICU and non-ICU admissions) and ICU-admissions (100.0%) (Table 29).

In the FAS, post first dose, VE estimates were 80.0% for hospitalizations, 75.7% for ICU admissions, and 100.0% for mortality.

For potential issues affecting the efficacy evaluation, refer to Section 11.7.1.

Table 29 Summary of Exploratory Efficacy Endpoint Analysis Results

Analysis Set: Endpoint	AZD1222	Placebo	Vaccine Efficacy (%)	(95% CI)
FVS: COVID-19 hospitalization occurring ≥15 days after the second dose [a]				
n/N (%)	1/17662 (<0.1)	8/8550 (<0.1)	94.15	(53.27, 99.27)
Total follow-up time (1000 person-years)	2.05	0.96	NA	NA
Incidence rate (cases per 1000 person-years)	0.49	8.32	NA	NA
FAS, seronegative at Baseline: COVID-19 hospitalization occurring post first dose [b]				
n/N (%)	7/20589 (<0.1)	17/10300 (0.2)	79.99	(51.76, 91.70)
Total follow-up time (1000 person-years)	4.47	2.17	NA	NA
Incidence rate (cases per 1000 person-years)	1.57	7.83	NA	NA
FVS: COVID-19-related ICU admission occurring ≥15 days after second dose [a, c]				
n/N (%)	0/17662 (0)	1/8550 (<0.1)	100	(-1781.58, NE)
Total follow-up time (1000 person-years)	2.05	0.96	NA	NA
Incidence rate (cases per 1000 person-years)	0	1.04	NA	NA
FAS, seronegative at baseline: COVID-19-related ICU admission occurring post first dose [b]				
n/N (%)	2/20589 (<0.1)	4/10300 (<0.1)	75.67	(-32.83, 95.54)
Total follow-up time (1000 person-years)	4.47	2.17	NA	NA
Incidence rate (cases per 1000 person-years)	0.45	1.84	NA	NA

Analysis Set: Endpoint	AZD1222	Placebo	Vaccine Efficacy (%)	(95% CI)
FAS, seronegative: COVID-19 death from Day 1 to Day 730 [b, c, d]				
n/N (%)	0/20589 (0)	2/10300 (<0.1)	100	(-166.41, NE)
Total follow-up time (1000 person-years)	4.47	2.17	NA	NA
Incidence rate (cases per 1000 person-years)	0	0.92	NA	NA
FAS, seronegative: All-cause mortality from Day 1 to Day 730 [b, d]				
n/N (%)	7/20589 (<0.1)	7/10300 (<0.1)	51.37	(-38.66, 82.95)
Total follow-up time (1000 person-years)	4.47	2.17	NA	NA
Incidence rate (cases per 1000 person-years)	1.57	3.22	NA	NA

[a] The observation period for the endpoint was 15 days post second dose up to 1 year in study, or up to the date of the intercurrent event. An intercurrent event was defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and was treated as no event. Total follow-up time was the sum of the observation periods over all participants in the study arm divided by 1000.

[b] The observation period for the endpoint was post first dose up to 1 year in study, or up to the date of the intercurrent event. An intercurrent event was defined as study discontinuation/unblinding/authorized COVID-19 vaccine administration prior to meeting the criteria for efficacy endpoint and was treated as no event. Total follow-up time was the sum of the observation periods over all participants in the study arm divided by 1000.

[c] The VE of AZD1222 versus control and the exact 1-sided 97.5%CI were estimated based on stratified Poisson regression with exact conditional method (including study arm as factor, stratification factor [age group at informed consent] as strata factor as well as the log of total number of participants for each combination of study arm and strata as an offset).VE was defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio was from the stratified Poisson regression with exact conditional method. The 1-sided 97.5%CI for the VE was obtained by taking 1 minus the 1-sided 97.5%CI of the risk ratio derived from the model.

[d] None of the participants had yet reached Day 730.

Note: The VE of AZD1222 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study arm as a factor, stratification factor [age group at inform consent] as covariate as well as the log of the follow-up time as an offset).

Note: The VE was defined as 1-(incidence from the AZD1222 arm / incidence from the placebo arm), where the risk ratio was from the Poisson regression model with robust variance. The 95% CI for the VE was obtained by taking 1 minus the 95% CI of the risk ratio from the model.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Note: COVID-19 endpoints were based on adjudicated events.

CI = confidence interval; COVID-19 = coronavirus disease-2019; FAS = full analysis set; FVS = fully vaccinated analysis set; ICU = intensive care unit; NA = not applicable; NE = not evaluable; VE = vaccine efficacy.

Source: Tables 14.2.1.3.1.2, 14.2.1.3.3.2, 14.2.1.3.4.2, 14.2.1.3.4.4, 14.2.1.3.3.4, and 14.2.1.3.2.2

For the endpoints summarized in Table 29, additional time to first analyses were conducted as well as graph presentations for cumulative incidence of each event type. These outputs are provided in Section 14.2, and shown in Table 30.

Table 30 Additional Summary Tables and Figures Related to Exploratory Endpoints

Table Number	Title
All-cause mortality	
Table 14.2.1.3.1.1	Time to All-cause Mortality from Day 1 Through Day 730 (Full Analysis Set for Participants Who are Seronegative at Baseline)
Figure 14.2.1.3.1.1	Cumulative Incidence of All-cause Mortality from Day 1 Through Day 730 (Full Analysis Set for Participants Who are Seronegative at Baseline)
COVID-19 related mortality	
Table 14.2.1.3.2.1	Time to COVID-19-related Mortality from Day 1 Through Day 730 (Full Analysis Set for Participants Who are Seronegative at Baseline)
Figure 14.2.1.3.2.1	Cumulative Incidence of COVID-19-related Mortality From Day 1 Through Day 730 (Full Analysis Set for Participants Who are Seronegative at Baseline)
COVID-19-related Hospitalization Occurring ≥ 15 Days Post Second Dose of Study Intervention	
Table 14.2.1.3.3.1	Time to First COVID-19-related Hospitalization Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Analysis Set)
Figure 14.2.1.3.3.1	Cumulative Incidence of First COVID-19-related Hospitalization Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Analysis Set)
COVID-19-related Hospitalization Occurring Post First Dose of Study Intervention	
Table 14.2.1.3.3.3	Time to First COVID-19-related Hospitalization Occurring Post First Dose of Study Intervention (Full Analysis Set for Participants Who are Seronegative at Baseline)
Figure 14.2.1.3.3.3	Cumulative Incidence of First COVID-19-related Hospitalization Occurring Post First Dose of Study Intervention (Full Analysis Set for Participants Who are Seronegative at Baseline)
COVID-19-related ICU Admission Occurring ≥ 15 Days Post Second Dose of Study Intervention	
Table 14.2.1.3.4.1	Time to First COVID-19-related ICU Admission Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Analysis Set)
Figure 14.2.1.3.4.1	Cumulative Incidence of First COVID-19-related ICU Admission Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Analysis Set)
COVID-19-related ICU Admission Occurring Post First Dose of Study Intervention	
Table 14.2.1.3.4.3	Time to First COVID-19-related ICU Admission Occurring Post First Dose of Study Intervention (Full Analysis Set for Participants Who are Seronegative at Baseline)
Figure 14.2.1.3.4.3	Cumulative Incidence of First COVID-19-related ICU Admission Occurring Post First Dose of Study Intervention (Full Analysis Set for Participants Who are Seronegative at Baseline)

11.1.3.1 Viral Genome Copies in NP Swabs Collected at Illness Visits as Determined by qRT-PCR

Limited data were available for quantitative analyses of viral loads as of the 05 Mar 2021 data cut-off date. In order to generate robust conclusions, these data will be examined for the

6 -month post second dose analysis. Cumulative data will be provided in a forthcoming CSR addendum.

11.1.3.2 Genotypic Analysis of SARS-CoV-2 from NP Swabs Collected on Day 1 Illness Visit

The frequency of SARS-CoV-2 variants was investigated in Study D8110C00001 by two modalities:

- Whole genome sequencing in saliva samples to assess variants by lineages (and clades) and
- Next generation sequencing of the Spike protein from NP swabs to assess the individual amino acid changes observed in the Spike protein.

For whole genome sequencing, frequencies of lineages and clades were assessed in the FAS using the first positive saliva sample from study participants who collected shedding specimens as part of Illness Visits (not collected in Chile and Peru) (see IEMT Tables 346.1 and 346.3). Whole genome NGS was performed utilizing the Illumina COVIDSeq Test and software, which identified lineage and clade of the recovered SARS-CoV-2 (Rambaut et al 2020, Hodcroft et al 2021). As of March 2020, over 900 SARS-CoV-2 lineages have been identified in the Pango lineage nomenclature system (Rambaut et al 2020). Conversely, only 7 Nextstrain clades are circulating with frequencies of > 5% (Hodcroft et al 2021). Given the larger amount sequence breadth required to make a lineage designation for SARS-CoV-2 (as compared to clade), approximately 30% of the 359 available sequences had no identifiable lineage. The clade of all 359 sequences was determined.

A limited number of variants of concern were identified within the FAS who were seronegative at baseline as of the data cut-off date (05 March 2021). Two cases of B.1.1.7 (Alpha) were observed, and one case of B.1.351 (Beta) was identified (another probable B.1.351 case was identified by clade designation, as 20H/501Y.V2, see IEMT Table 346.3). No cases of lineage B.1.1.28.1 (ie, P.1; Gamma) were identified through sequencing of saliva samples. Of the WHO designated Variants of Interest, B.1.427, B.1.429, and B.1.526 (Iota) were observed in the FAS, with B.1.429 being the most frequent (with 14 cases observed). No cases of the B.1.617.1 lineage (Kappa) or the B.1.617.2 (Delta) lineage were detected. A majority of cases identified in the study, were of lineage B.1.2 (134 cases). Additional prevalent lineages were B.1 (31 cases), B.1.234 (11 cases), and B.1.243 (9 cases) (see IEMT Table 346.1). At the clade level, 20G was the predominant clade (150 cases), followed by 20A, 20C, 19A, and 20B. Minimal cases of 20D, and 20F were observed (see IEMT Table 346.3).

While multiple lineages were seen, still further heterogeneity was determined by investigating the Spike-specific amino acid changes present within virus recovered from NP swabs. The Spike sequence at a 25% consensus cut-off showed D614G to be the most prevalent mutation

within observed variants, however the common Spike mutations observed with the B.1.427/B.1.429 lineages (S13I:W152C:L452R:D614G) were identified frequently, as was the dual D614G:P681H mutations that may be responsible for improved transmissibility (Lasek-Nesselquist et al 2021). These data also allowed the inclusion of sequences from Chile and Peru where numerically reduced VE was observed. Mutations associated with the P.1 variant were not observed in any country, including Chile and Peru. Of note, 5 cases with mutational patterns consistent with the C.37 lineage (Lambda) were identified in Peru (see IEMT Table 346.5). Future analyses of Spike variants will include a Pango lineage set designation as determined by Spike only sequences (O'Toole et al 2021).

Vaccine efficacy of variants was also evaluated using the FVS for those adjudicated cases of COVID-19 that occurred ≥ 15 days post second dose of study (Table 31, Table 32). Of the 203 adjudicated cases included in the participants meeting the primary endpoint using the primary efficacy analysis dataset (see Section 11.1.1.1), sequencing data was available for 146 cases (ie, 71.9%) to examine the VE associated with variants (see IEMT Table 346.8). Of these sequences, 66 (32.5%) included both sequences from saliva specimens (where clade and lineage are identified) and Spike NGS from NP swabs.

A total of 88 of the 203 adjudicated cases in the FVS had interpretable lineage data available, and the resulting VE estimate (95% CI) within this subgroup 77.2% [64.48, 85.40]) was consistent with the primary efficacy analysis (Table 31). Among participants for whom there was either insufficient sequence coverage for lineage designation or sequence data was not obtained from a saliva sample, the VE estimate (70.7% [39.72, 85.80]) was also consistent with the primary efficacy analysis, thereby suggesting that the result for the VE estimate among those participants with sequence data was representative of the study population. Caution is warranted in the interpretation of VE estimates within individual variants as the sample size and wide CIs preclude definitive conclusions. However, of the most frequent lineages observed, B.1.2, B.1, and B.1.429 VE was generally consistent with the overall VE estimate (VE [95% CI] = 71.1% [49.37, 83.44], 76.8% [7.40, 94.21], and 65.3% [-55.23, 92.23], respectively). Analysis of VE estimate by clade was also conducted and, the results were directionally consistent with the overall observed VE estimate (see IEMT Table 346.4).

Interpretable Spike NGS sequencing data (NP swabs) were available for 101 of the 203 cases in the FVS, and the resulting VE estimate (95% CI) within this subgroup (74.9% [61.35, 83.66]) was consistent with the primary efficacy analysis (Table 32). There were 4 variants with mutational patterns consistent with Variants of Concern (two putative B.1.351 and two putative B.1.1.7 variants were observed); however, there were 7 cases with mutational patterns consistent with the Variants of Interest B.1.427/B.1.429. In a variant that expressed the S13I:W152C:L452R:D614G amino acid changes (present within B.1.427 and B.1.429 lineages), VE was numerically lower at 53.7%, however there were wide CIs

(95% CI:-129.57, 90.65). Given the VE estimates observed in the variant VE as determined by WGS in saliva (ie, B.1.429 VE [95% CI] = 65.3% [-55.23, 92.23]) were still consistent with overall AZD1222 VE, it would be assumed this is a reflection of low sample size rather than reduced efficacy against these variants.

A variant with a large deletion in the NTD as well as multiple RBD substitutions (G75V:T76I:R246N:S247-:Y248-:L249-:T250-:P251-:G252-:D253-:L452Q:F490S:D614G:T859N) later designated as the C.37 lineage (Lambda) was detected in 4 cases in Peru (3 in the AZD1222 group and 1 in placebo group) (VE of -39.50% [95% CI: -1235.77, 85.55]). Further, another case with a similar mutational pattern also occurred in the AZD1222 arm in Peru. Further phenotypic characterization of the neutralizing potency of sera against AZD1222 vaccinated individuals against a Lambda variant pseudovirus is ongoing and will be reported separately from this CSR.

Table 31 Summary of SARS-CoV-2 Variants by Lineage, Whole Genome NGS of Saliva Samples using Adjudicated cases Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Set)

SARS-CoV-2 Lineages	Whole Genome Next-Generation Sequencing, n (%)			Vaccine Efficacy (95% CI)
	AZD1222 (N = 17662)	Placebo (N = 8550)	Total (N = 26212)	
Total adjudicated cases	73 (0.41)	130 (1.52)	203 (0.77)	73.98 (65.34, 80.47)
Adjudicated cases with variant data available, n (%)	29 (0.16)	59 (0.69)	88 (0.34)	77.23 (64.48, 85.40)
Variants of concern				
B.1.1.7 (Alpha)	1 (0.01)	1 (0.01)	2 (0.01)	53.68 (-640.38, 97.10)[#]
B.1.351 (Beta)	1 (0.01)	0	1 (0.00)	-inf (NE, 98.76)[$]
B.1.1.28.1 (Gamma)	0	0	0	NA
Variants of interest				
B.1.525 (Eta)	0	0	0	NA
B.1.526 (Iota)	0	0	0	NA
B.1.427 (Epsilon)	0	1 (0.01)	1 (0.00)	100 (-1781.58, NE)[$]
B.1.429 (Epsilon)	3 (0.02)	4 (0.05)	7 (0.03)	65.27 (-55.23, 92.23)
B.1.1.28.2 (Zeta)	0	0	0	NA
Others with at least 5 participants overall				
B.1	3 (0.02)	6 (0.07)	9 (0.03)	76.84 (7.40, 94.21)[#]
B.1.2	20 (0.11)	32 (0.37)	52 (0.20)	71.05 (49.37, 83.44)
Adjudicated cases with no sequence result, n (%) [a]	12 (0.07)	19 (0.22)	31 (0.12)	70.74 (39.72, 85.80)
Adjudicated cases not sequenced, n (%) [b]	32 (0.18)	52 (0.61)	84 (0.32)	71.49 (55.71, 81.65)

[a] Insufficient sequence coverage for lineage designation.

[b] Participants who were not sequenced for a saliva sample.

Note: The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance (including study arm as a factor and stratification factor [age group at screening (18-65 years, >=65 years)].

#: The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance including study arm as a factor.

$: The maximum likelihood estimate of VE of AZD1222 versus control and the exact 95% CI (or 97.5% 1-sided) were estimated based on stratified Poisson regression with Exact Conditional Method including treatment as factor, age group at screening (18-65 years, >=65 years) as strata factors as well as the log of total number of participants for each combination of treatment and strata. If the maximum likelihood estimate of VE is 100% or negative infinity, the exact 97.5% 1-sided CI is reported.

CI = confidence interval; NA = not applicable; NE = not evaluable; NGS = next generation sequencing; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: Study D8110C00001 IEMT Table 346.2

Table 32 Summary of SARS-CoV-2 Variants by Spike Mutation, Spike-specific NGS of NP Swab Samples using Adjudicated cases Occurring ≥ 15 Days Post Second Dose of Study Intervention (Fully Vaccinated Set)

SARS-CoV-2 Lineages	Spike-specific Next-Generation Sequencing, n (%)			Vaccine Efficacy [a] (95% CI)
	AZD1222 (N = 17662)	Placebo (N = 8550)	Total (N = 26212)	
Total adjudicated cases	73 (0.41)	130 (1.52)	203 (0.77)	73.98 (65.34, 80.47)
Adjudicated cases with variant data available, n (%)	32 (0.18)	59 (0.69)	91 (0.35)	74.87 (61.35, 83.66)
Variants of concern				
D80A:D215G:L241-:L242-:A243-:H245Y:K417N:E484K:N501Y:D614G:A701V [b]	1 (0.01)	0	1 (0.00)	NA
T19I:D80A:D215G:L241-:L242-:A243-:K417N:E484K:N501Y:D614G:A701V [b]	1 (0.01)	0	1 (0.00)	NA
H69-:V70-:Y144-:G261V:N501Y:A570D:D614G:P681H:T716I:S982A:D1118H [c]	0	1 (0.01)	1 (0.00)	NA
H69-:V70-:Y144-:N501Y:A570D:D614G:P681H:T716I:S982A:D1118H:K1191N [c]	0	1 (0.01)	1 (0.00)	NA
Variants of interest				
S13I:W152C:L452R:D614G [d]	3 (0.02)	3 (0.04)	6 (0.02)	53.68 (-129.57, 90.65)
S13I:H49H/Y:W152C:L452R:S459P/S:D614G [d]	0	1 (0.01)	1 (0.00)	NA
Mutations with at least 3 participants				
D614G	10 (0.06)	18 (0.21)	28 (0.11)	74.26 (44.22, 88.12)
D614G:P681H	2 (0.01)	4 (0.05)	6 (0.02)	76.86 (-26.33, 95.76)
G75V:T76I:R246N:S247-:Y248-:L249-:T250-:P251-:G252-:D253-:L452Q:F490S:D614G:T859N H69-:V70-:D614G [e]	3 (0.02)	1 (0.01)	4 (0.02)	-38.95 (-1235.77, 85.55)[#]
Adjudicated cases with no sequence result, n (%) [f]	0	0	0	NA
Adjudicated cases not sequenced, n (%) [g]	41 (0.23)	71 (0.83)	112 (0.43)	73.25 (60.71, 81.79)

[a] The VE was only calculated when ≥ 3 events were reported.

[b] Mutation is commonly associated with B.1.351 (Beta).

[c] Mutation is commonly associated with B.1.1.7 (Alpha).

[d] Mutation is commonly associated with B.1.427 and B.1.429 (Epsilon).

[e] All cases occurred in Peru. This lineage was later designated as the C.37 lineage (Lambda).

[f] Insufficient sequence coverage for Spike mutation designation.

[g] Participants who were not sequenced by Spike NGS (ie, no NP swab).

Note: The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance (including study arm as a factor and stratification factor [age at inform consent].

#: The VE of AZD1222 versus placebo and the 95% CI were estimated based on Poisson regression with robust variance including study arm as a factor.

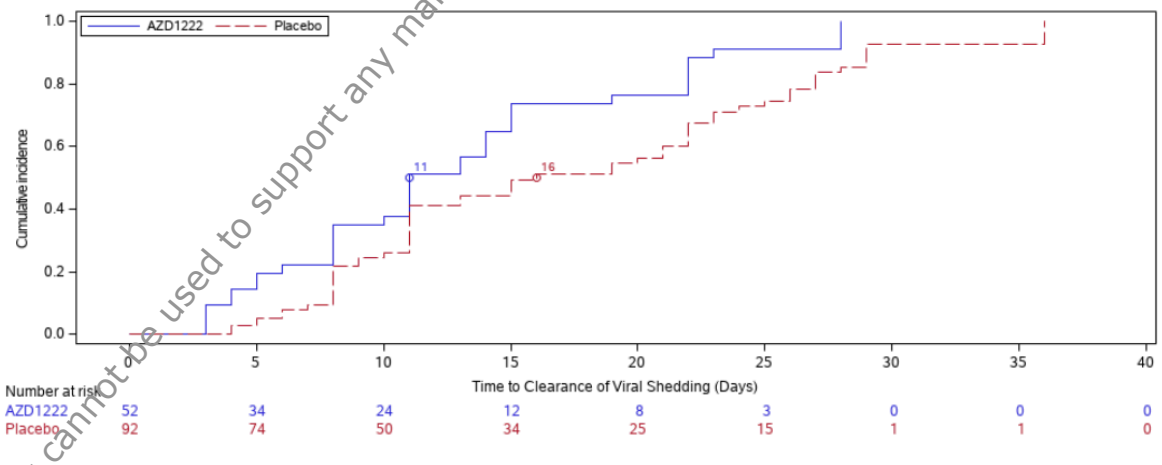
CI = confidence interval; NA = not applicable; NGS = next generation sequencing; NP = nasopharyngeal; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

Source: IEMT Table 346.6

11.1.3.3 Duration of SARS-CoV-2 Shedding in Saliva Over Time

The impact of AZD1222 on viral shedding was assessed in saliva samples collected at Illness Visits. Participants presenting at sites with qualifying symptoms self-collected (either at home or at clinical sites) saliva samples at eight time points between illness D1 and illness D28 to assess how long SARS-CoV-2 could be detected in saliva. When the time to clearance of SARS-CoV-2 was assessed in the subset of participants receiving 2 doses of the investigational product (ie, in both the IAS and FVS), where the infection began at least 15 days post second dose, time to clearance of SARS-CoV-2 in saliva samples in AZD1222 vaccinated participants was notably shorter (median 11 vs 16 days) compared with participants in the placebo group (Figure 9). These data suggest that in addition to reducing the incidence of COVID-19 disease, even in those study participants who have breakthrough infections, SARS-CoV-2 is shed for a shorter amount of time in AZD1222 recipients, reducing the length of time vaccinated individuals are capable of transmitting infection. These data are consistent with data from the University of Oxford sponsored study, COV002, in which nasal and throat swabs were self-collected by study participants throughout the course of the trial where reduction in the duration of shedding and viral load were observed (Emary et al 2021). When the time to clearance of SARS-CoV-2 was assessed in participants receiving any dose of the investigational product (ie, in the IAS), the time to clearance of SARS-CoV-2 in saliva samples in AZD1222 vaccinated participants was not notably reduced (14 vs 15 days) (see IEMT Figure 305.2).

Figure 9 Cumulative Incidence of Clearance for Shedding (Immunogenicity Analysis Set and Fully Vaccinated Set)



Note: Time to Clearance of Viral Shedding = (Date of Illness Visit when viral shedding first tested as persistently negative or date of last Illness Visit when test was positive, if no negative test available) –Date of first positive + 1.

Note: If a participant had multiple sets of Illness Visits, the first set of Illness Visits with a positive RT-PCR test result was used for the summary.

Note: The median time to clearance of viral shedding for each group is marked by a circle.

Source: IEMT Figure 369.1.

11.1.3.4 Symptoms Recorded by Participants in an Illness e-Diary from Illness Visits Day 2 through Day 28

At each Illness Visit, participants recorded symptoms in an Illness e-Diary from Illness Visits Day 2 through Day 28. Symptoms from the first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose were summarized for the FVS. Illness Visits in the FVS were conducted in 70 participants in the AZD1222 group and 103 participants in the placebo group (Table 14.2.1.3.8). In the AZD1222 group, the most commonly recorded symptoms included congestion (63 participants [90.0%]), runny nose (53 participants [75.7%], and fatigue (52 participants [74.3%]). In the placebo group, the most commonly reported symptoms included fatigue (92 participants [89.3%]), congestion (90 participants [87.4%]), and headache (88 participants [85.4%].

11.2 Pharmacokinetic Results- Not Applicable

Not applicable.

11.3 Pharmacodynamic Results- Not Applicable

Not applicable.

11.4 Pharmacokinetic/Pharmacodynamic Relationship-Not Applicable

Not applicable.

11.5 Immunogenicity

Summary tables and figures pertaining to this section are presented in Section 14.2 (Table 14.1.9.2, Table 14.1.9.3, and Figure 14.2.1.3.7.1) and Appendix 16.2.

For potential issues affecting the efficacy evaluation, refer to Section 11.7.1.

11.5.1 Humoral Immune Responses

The humoral immunogenicity of AZD1222 for the overall IAS was determined using validated bioanalytical methods to assess S-binding, RBD-binding, and pseudoneutralizing antibodies. Overall, AZD1222 generated a robust humoral response.

Limited data were available on humoral immunogenicity of participants with SARS-CoV-2 infections (and collected at Illness Visits); these data will be investigated further for the 6-month post second dose analysis and provided in a CSR addendum.

11.5.1.1 Antibody Responses to AZD1222 S Antigen

Geometric mean titers of S-binding and RBD-binding antibodies peaked at 14 days post second dose (24224.11 AU/mL and 29487.39 AU/mL, respectively) of AZD1222 and were

maintained above the levels achieved by the first dose through D90 (Table 14.2.2.1.1.1). Minimal data were available at D180; therefore, durability of immunogenicity will be further investigated for the 6-month post second dose analysis and provided in a CSR addendum. Importantly, baseline seronegative and seropositive participants also had increased S-binding and RBD-binding responses to AZD1222 vaccination (Table 14.2.2.1.1.2).

Antibody responses to AZD1222 S antigen were further stratified by age, race, and with longer dose intervals. Spike-binding antibodies were detectable 14 days after the first dose of AZD1222 (median of 1972 AU/mL) and further increased after a second dose, peaking 14 days after a second dose (median of 25244 AU/mL) (Figure 10).

Given numerically lower VE estimates were observed in study participants of American Indian or Alaska Native origin, S-binding antibody responses were assessed by race. Overall, no decreases in immunogenicity were observed in Black, American Indian/Alaska native, or 'other' races (a combination of Asian, Native Hawaiian or Pacific Islander, Multiple races); indeed, median S binding titers were numerically higher in non-White participants (see IEMT Figure 305.4.2). Notably, study participants from Chile and Peru did not participate in the Substudy on immunogenicity and reactogenicity, therefore no data were available from Latin American participants who identify as American Indians as of the 05 March 2021 data cut-off date.

S-binding antibody response was additionally examined by age at enrollment. Minimal but numerically lower humoral antibody responses were observed in those ≥ 65 years of age (see IEMT Figure 305.4.3). However, given that the VE estimate was similar in participants ≥ 65 years of age as compared to those 18-64 years of age, it is unlikely that these differences are clinically meaningful. Duration of immunogenicity and protection from COVID-19 will continue to be investigated for the 6-month post second dose analysis and will be provided in a CSR addendum.

A subanalysis of S-binding antibody response was performed in study participants who were affected by a clinical hold (n = 804 in the IAS) as compared with those who were not affected by a clinical hold. S-binding antibody response was not reduced in participants with dose intervals of > 4 weeks due to a clinical hold, with median titers of 27495 and 24489 AU/mL at D43 for the participants affected and not affected by the clinical hold, respectively (Figure 10).

11.5.1.2 Anti-SARS-CoV-2 Neutralizing Antibody Levels

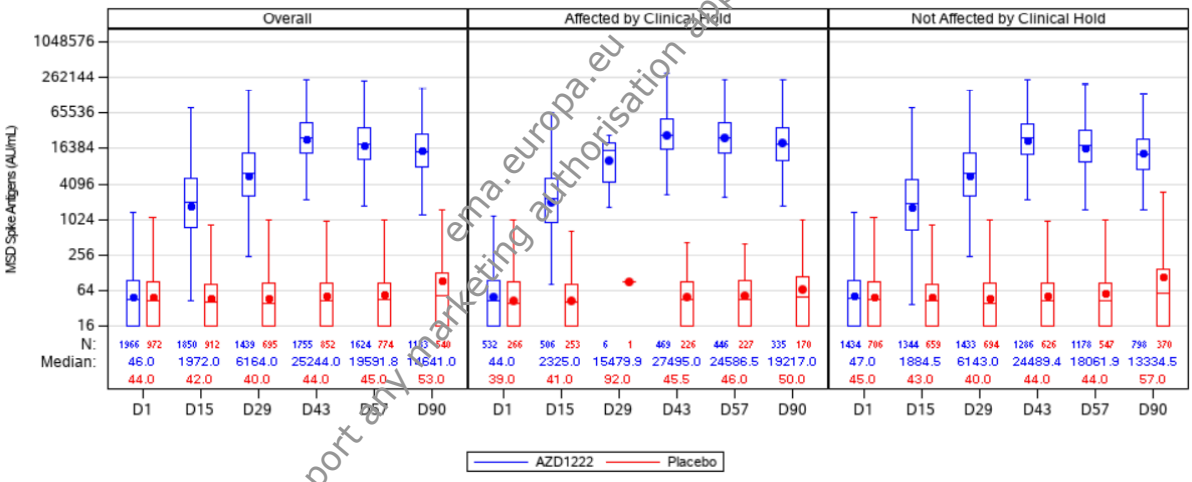
Pseudoneutralizing antibody responses were elevated above baseline at 14 days post first dose of AZD1222 (GMT = 41.37 AU/mL) but had slightly different kinetics of induction as compared to S binding responses, with responses peaking at 28 days post second dose (GMT = 245.56 AU/mL) instead of at 14 days post second dose (Table 14.2.2.2.1.1).

Pseudoneutralizing antibody responses were also elevated in seronegative and seropositive participants after the first and second doses of AZD1222 (Table 14.2.2.2.1.2).

Neutralizing antibody response was further stratified by age, race, and with longer dose intervals. Neutralizing antibody responses had similar kinetics of induction as antibody responses to AZD1222 S antigen, although median titers were not raised over baseline at D15 due to a lower sensitivity associated with the pseudoneutralization assay as compared to the S-binding antibody assay (Figure 11).

A similar trend was seen when neutralizing antibodies were assessed by race, ethnicity, and clinical hold status as the data from S-binding antibody responses (see IEMT Figure 305.5.2 and Figure 11).

Figure 10 Quantification of SARS-CoV-2 S-binding Antibody Levels by Dosing Interval for Immunogenicity Analysis Set (AZD1222 Group, Seronegative at Baseline)



Note: The bottom and top edges of the box indicate the first and third quartiles (the difference is the IQR), the line inside the box is the median, and the marker inside the box is the geometric mean. Any points more than 1.5 x IQR from the box are considered outliers and are not displayed. The whiskers that extend from the box indicate the minimum and maximum after removing the outliers. Boxplots were created using the log-normal distribution.

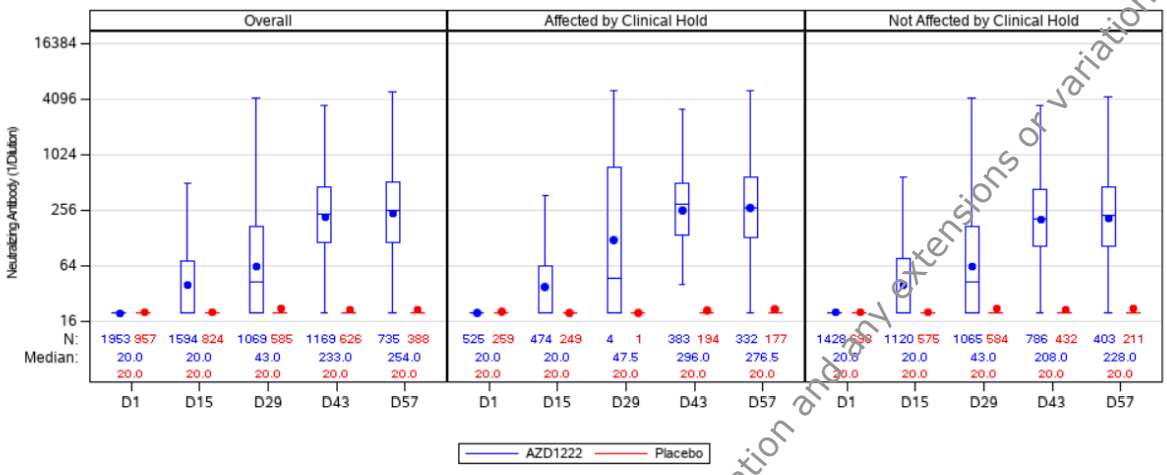
Note: The value at D1 was the last non-missing value taken prior to the first dose.

Note: Titer values measured as below LLoQ (33) were imputed to a value that was half of the LLoQ. Titer values measured as above ULoQ (2000000) were imputed at the ULoQ value.

D = Day; MSD=Meso Scale Discovery, LLoQ = Lower Limit of Quantification, IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome coronavirus disease-2019; ULoQ = Upper Limit of Quantification.

Source: IEMT Figure 305.4.1.

Figure 11 Quantification of SARS-CoV-2 nAb Levels (Pseudoneutralization) by Dosing Interval for Immunogenicity Analysis Set (AZD1222 Group, Seronegative at Baseline)



Note: The bottom and top edges of the box indicate the first and third quartiles (the difference is the IQR), the line inside the box is the median, and the marker inside the box is the geometric mean. Any points more than 1.5 x IQR from the box are considered outliers and are not displayed. The whiskers that extend from the box indicate the minimum and maximum after removing the outliers. Boxplots were created using the log-normal distribution.

Note: The value at D1 was the last non-missing value taken prior to the first dose.

Note: Titer values measured as below LLoQ (40) were imputed to a value that was half of the LLoQ. Titer values measured as above ULoQ (787339) were imputed at the ULoQ value.

D = Day; LLoQ = Lower Limit of Quantification; IQR = interquartile range; nAb = neutralizing antibody; SARS-CoV-2 = severe acute respiratory syndrome coronavirus disease-2019; ULoQ = Upper Limit of Quantification.

Source: IEMT Figure 305.5.1.

11.5.2 Anti-vector Responses to ChAdOx-1 Adenovirus Vector

Anti-vector responses were evaluated by a validated bioanalytical method in a subgroup of study participants at the 05 March 2021 data cut-off date. Geometric mean titers of anti-ChAdOx nAbs were similar between the placebo (26.27 AU/mL) and AZD1222 groups (25.35 AU/mL) at baseline and minimally raised above the lower limit of quantification, suggesting low baseline seropositivity to the ChAdOx1 vector. In AZD1222 vaccinated participants, anti-vector responses were dramatically increased 28 days post first dose (1101.48 AU/mL), with similar titers 28 days post second dose (1168.97 AU/mL) (Table 14.2.2.6.1.1).

11.6 Pharmacogenetic Results- Not Applicable

Not applicable.

11.7 Potential Issues Affecting the Efficacy Evaluation

11.7.1 Statistical/Analytical Issues

- Due to the availability of EUA vaccines during the study, participants were unblinded to randomized treatment assignment to allow an informed decision as to whether the participant should receive an EUA vaccination. To ensure that comparisons between the AZD1222 and placebo study arms were performed based on double-blind assessments, all efficacy, safety, and immunogenicity analyses were censored at the time of unblinding or EUA vaccination, whichever occurred first. To evaluate the impact of unblinding on the primary efficacy endpoint, sensitivity and supplementary analyses were conducted. The primary efficacy endpoint analysis based on the Poisson regression with robust variance [VE 74.0%; 95% CI 65.34, 80.47], the supportive analysis based on the Cox proportional hazards regression [VE 73.89%; 95% CI 65.34, 80.48], the sensitivity analysis using the MI approach [VE 73.3%; 95% CI 64.59, 79.85] under the assumption of missing at random, and the supplementary analysis without censoring at unblinding/EUA vaccination [VE 74.3%; 95% CI 66.04, 80.58], showed similar VE estimates. The primary efficacy endpoint conclusion appears to be robust to missing data regardless of the analysis method selected.
- Incidence of post-treatment response for SARS-CoV-2 nucleocapsid antibodies is derived for participants in the FVS regardless of whether the participant satisfied the case definition for the primary efficacy endpoint. Not all participants who met the case definition for the primary efficacy endpoint also met the post-treatment response endpoint based on SARS-CoV-2 nucleocapsid antibodies. Participants who met the primary efficacy endpoint but did not meet the post-treatment response endpoint generally had no SARS-CoV-2 nucleocapsid result available after Illness Visit 1 and prior to the data cut-off date or unblinding, and therefore, their post-treatment response was not detected. Given that the first positive SARS-CoV-2 nucleocapsid result for the majority of participants who had a post-treatment response occurred at Illness Visit 14, Illness Visit 28, or at a subsequent main study assessment, it is anticipated that the post-treatment response for these participants will be observed for the 6-month post second dose analysis when additional serology results are available.
- At time of the data snapshot on 29 April 2021, not all samples collected prior to the data cut-off date of 03 March 2021 had been analysed at the central laboratory for immunogenicity exploratory endpoints. In particular, viral load data from saliva and NP swabs collected at Illness Visits were sparse and the results summarized in this report should be interpreted with caution. Summaries for these exploratory endpoints will be refreshed for the 6-month post second dose analysis and provided in a forthcoming CSR addendum.
- Although subgroup analysis results are presented for the primary efficacy endpoint as well as key secondary endpoints, the study was not designed to achieve statistical power for these comparisons. Some subgroups, had low sample sizes and correspondingly low number of events available for analysis, resulting in wide CIs. Results from these subgroup analyses should be interpreted with caution.
- For some secondary and exploratory COVID-19 related endpoints, the number of observed events was low and the Poisson regression with robust variance failed to

converge. As pre-specified in the SAP, a stratified exact Poisson regression model was to be used when the Poisson regression with robust variance failed to converge. In the extreme case when the AZD1222 study arm has no observed events and the placebo arm has ≥ 1 observed event, the maximum likelihood estimate (MLE) for the rate ratio is zero, corresponding to VE = 100%, however PROC GENMOD gives a median unbiased estimate instead of the MLE and defaults to a 1-sided 95% CI since the upper confidence limit of VE cannot be estimated. In such cases, the VE was set to the MLE (100%), and a 1-sided 97.5% CI was presented for completeness. The inverse was treated similarly, when there were 0 events in the placebo arm and ≥ 1 event in the AZD1222 arm, the VE was set to - Infinity and the 1-sided 97.5% CI was presented.

- Non-COVID-related death is a competing risk for the primary efficacy endpoint. Regardless of cause, all deaths were submitted to the adjudication committee for independent blinded review and categorized as COVID-19-related or not. As such, all deaths adjudicated as related to COVID-19 were included as a primary efficacy endpoint event and deaths adjudicated as not related to COVID-19 were treated as intercurrent events and therefore censored at the date of death. Given that all deaths were independently adjudicated, it was assumed that deaths which were confirmed as unrelated to COVID-19 were independent of the time of COVID-19.

11.8 Efficacy Evaluation Conclusions

Duration of follow up

- As of the data cut-off date of 05 March 2021, regardless of unblinding events, the median durations of follow up in the FAS from the second dose in both the AZD1222 group and placebo group were approximately 60 days; and the median duration of follow up from first dose was approximately 90 days.

Primary efficacy endpoint

- In the primary efficacy analysis using 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 RT-PCR-positive symptomatic illness, with a lower bound of the 95.0% CI of 65.34% and a 2-sided nominal p-value of < 0.001 for testing H0: VE ≤ 30%, which met the pre-specified success criterion.
- Using the FVS, the primary endpoint result was robust to different imputation approaches for missing data and still met the pre-specified success criterion, including imputation using the higher placebo event rate.
- A series of 4 supplementary analyses were also conducted as pre-specified in the SAP. All 4 analyses demonstrated VE estimates that were consistent with the primary efficacy analysis (point estimates approximately 74.0%) and included time to first event and changes to which participants were included in the analysis (ie, analysis set, participants whose timing of the second dose was impacted by clinical hold, and contribution of different data that were considered during adjudication).
- Vaccine efficacy estimates across subgroups based on age, gender, ethnicity, BMI, and presence of pre-defined comorbidities were consistent with the VE estimate for the overall population.

Secondary efficacy endpoints

- All of the 4 key secondary endpoints were statistically significant using the hierarchical fixed sequence testing method and were analyzed for events ≥ 15 days post second dose:
  - First case of SARS-CoV-2 RT-PCR positive symptomatic illness regardless of evidence of prior SARS-CoV-2 infection (VE estimate [95% CI] of 73.7% [65.13, 80.13]).
  - Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness (VE estimate [95% CI] of 100.0% [71.62, NE] due to no cases in the AZD1222 group).
  - Incidence of COVID-19-related emergency department visits (VE estimate [95% CI] of 94.8% [58.98, 99.34]).
  - Incidence of the first post-treatment response for SARS-CoV-2 Nucleocapsid antibodies regardless of symptoms (VE estimate [95% CI] of 64.3% [56.05, 71.03]). (Note: confirmatory change to positive PCR was not required, only seroconversion.)
- Evaluation of efficacy using the CDC or University of Oxford-defined criteria resulted in consistent conclusions relative to the primary efficacy analysis (VE estimates [95% CI] of 69.7% [60.68, 76.57] and 70.7% [61.62, 77.64], respectively).
- Efficacy following first dose demonstrated a VE estimate (95% CI) of 54.5% (46.48, 61.26) against symptomatic illness and a VE estimate (95% CI) of 85.0% (58.97, 94.50) against severe or critical illness.

Exploratory efficacy endpoints

- At ≥ 15 days post second dose in the FVS, and post first dose in the FAS, respectively, high VE estimates were demonstrated for hospitalizations (94.2% and 80.0%, which includes ICU and non-ICU admissions) and ICU-admissions (100.0% and 75.7%).
- A total of 88 of the 203 cases in the FVS had interpretable lineage data available, and the resulting VE estimate (95% CI) within this subgroup was consistent with the primary efficacy analysis (77.2% [64.48, 85.40]). A total of 101 of the 203 cases in the FVS had interpretable Spike NGS sequencing data available, and the resulting VE estimate (95% CI) within this subgroup was also consistent with the primary efficacy analysis (74.9% [61.35, 83.66]). A small number of variants of concern or variants of interest were observed as of the data cut-off date (05 March 2021) by whole genome NGS of saliva samples and spike-specific NGS of NP swabs samples.
- When the time to clearance of SARS-CoV-2 was assessed in the subset of participants receiving 2 doses of the investigational product (ie, in both the IAS and FVS) where the infection began at least 15 days post second dose, time to clearance of SARS-CoV-2 in saliva samples in AZD1222 vaccinated participants was notably shorter (11 vs 16 days) compared with participants in the placebo group.

Immunogenicity endpoints

- Overall, AZD1222 generated a strong humoral response, including when stratified by age, race, and ethnicity.
- Spike-binding and RBD-binding antibodies peaked at 14 days post second dose of AZD1222 (GMTs of 24224.11 AU/mL and 29487.39 AU/mL, respectively) and were maintained above the levels achieved by the first dose through at least D90.
- Pseudoneutralizing antibody responses were elevated above baseline at 14 days post first dose of AZD1222 (GMT = 41.37 AU/mL) with responses peaking at 28 days post second dose (GMT = 245.56 AU/mL).

12. SAFETY EVALUATION

All safety analyses were performed by actual treatment received (AZD1222 versus saline placebo) using the SAF. As of the data cut-off date of 05 March 2021, all study participants who received at least 1 dose of study intervention were included in the SAF (see Section 9.8.2). The disposition of participants in the PAS for safety is presented in Figure 3. The demographic characteristics of the SAF were generally balanced among participants who received AZD1222 and the placebo treatments (see Table 14.1.4.1). For a description of the primary safety analyses, refer to Section 9.8.1.3.

12.1 Extent of Exposure

Summary tables and figures pertaining to this section are presented in Section 14.3.1 (see Table 14.1.1.1 and Table 14.3.1.1.3.1 through Table 14.3.1.1.3.3) and Appendix 16.2.

As of the data cut-off date of 05 March 2021, 99.8% of participants (32379 out of 32451 randomized participants; see Table 15) were included in the SAF based on actual study intervention received; 21587 participants received AZD1222 and 10792 participants received placebo (Table 33).

In the SAF, the proportion of participants at risk was balanced for all durations of follow up, with > 90% of participants having had at least 60 days of follow up post first dose (Table 33). Participants in the AZD1222 group in the SAF had a median duration of follow up post second dose of 61.0 days (range: 1 to 129 days) and participants had a median duration of follow up post first dose of 92.0 days (range: 1 to 190 days) regardless of unblinding events; the duration of follow up was similar for the placebo group.

In the SAF, results by age subgroup for follow-up time and participants at risk at each month post first study intervention were similar to the results for the overall SAF population (Table 14.3.1.1.3.2). In the AZD1222 group, regardless of unblinding events, participants ≥ 18 to < 65 years of age in the AZD1222 group had a median duration of follow up post second dose of 61.0 days (range: 1 to 129 days) and a median duration of follow up

post first dose of 92.0 days (range: 1 to 190 days). Participants ≥ 65 years of age had a median duration of follow up post second dose of 65.0 days (range: 1 to 129 days) and a median duration of follow up post first dose of 93.0 days (range: 8 to 188 days). In the placebo group, regardless of unblinding events, the duration of follow up in both age subgroups was similar to the AZD1222 group.

Table 33 Summary of Follow-up Time and Participants at Risk at Each Month After Each Dose (Safety Analysis Set)

Category	Statistic	AZD1222 N = 21587	Placebo N = 10792	Total N = 32379
of follow-up from first dose (days) Duration	n	21587	10792	32379
	Mean (SD)	93.5 (24.39)	92.7 (25.18)	93.2 (24.66)
	Median	92.0	91.0	92.0
	Min, max	1, 190	1, 189	1, 190
Duration of follow-up from second dose (days)	n	20773	9947	30720
	Mean (SD)	64.8 (21.42)	64.9 (21.71)	64.9 (21.52)
	Median	61.0	61.0	61.0
	Min, max	1, 129	1, 129	1, 129
Number and percentage of participants at risk from first dose				
Month 1 (Day 30)	n (%)	21505 (99.6)	10715 (99.3)	32220 (99.5)
Month 2 (Day 60)	n (%)	20153 (93.4)	9932 (92.0)	30085 (92.9)
Month 3 (Day 90)	n (%)	11256 (52.1)	5529 (51.2)	16785 (51.8)
Month 4 (Day 120)	n (%)	2288 (10.6)	1128 (10.5)	3416 (10.6)
Month 5 (Day 150)	n (%)	532 (2.5)	266 (2.5)	798 (2.5)
Month 6 (Day 180)	n (%)	529 (2.5)	266 (2.5)	795 (2.5)
Number and percentage of participants at risk from second dose				
Month 1 (Day 30)	n (%)	19842 (91.9)	9468 (87.7)	29310 (90.5)
Month 2 (Day 60)	n (%)	11525 (53.4)	5527 (51.2)	17052 (52.7)
Month 3 (Day 90)	n (%)	2331 (10.8)	1141 (10.6)	3472 (10.7)
Month 4 (Day 120)	n (%)	480 (2.2)	238 (2.2)	718 (2.2)

Note: Percentages were based on the number of participants in the analysis set by study arm.
Note: Follow-up time was regardless of unblinding events.
Max = maximum; min = minimum; SD = standard deviation.
Source: Table 14.3.1.1.3.1

12.2 Adverse Events

Summary tables and figures pertaining to this section are presented in Section 14.3.2 (see Table 14.3.1.1.1.1 through Table 14.3.1.4.4.6) and Appendix 16.2.

Solicited and unsolicited AEs, SAEs, and AESIs were reviewed using the SAF. All AEs were considered unsolicited AEs (collected by 'open question' at study visits) unless they were categorized as solicited AEs recorded in the Substudy only. Selected AE parameters were also reviewed by subgroup for age at randomization, race, gender (male and female), country, comorbidity at baseline, and baseline serostatus using the SAF. See Section 9.8.1.3 for additional detail on subgroup analyses.

12.2.1 Categories of Adverse Events

12.2.1.1 Overview of Solicited Adverse Events (Substudy)

Solicited AEs were local or systemic pre-defined events for assessment of reactogenicity. Solicited AEs were collected in a solicited AE e-diary only for participants in the Substudy (Table 7) and were assessed separately from the (unsolicited) AEs collected during the study. Participants were instructed to record the timing and severity of local and systemic solicited AEs, if applicable, for 7 days following administration of each dose of study intervention; for further detail, see Section 9.1. Some nonserious unsolicited AEs were incorrectly recorded as solicited AEs; for further detail, see Section 9.9.1 and Section 12.2.1.2. For an overall summary of solicited AEs for the SAF within 7 days post first dose, second dose, or any dose, see Table 34.

In the SAF, a total of 1956 participants in the AZD1222 group and 981 participants in the placebo group were evaluated for solicited AEs within 7 days after any dose. Within the first 7 days following any dose with AZD1222, solicited local and systemic AEs were reported by 74.1% (1440 participants) and 71.6% (1395 participants), respectively. In the placebo group, solicited local and systemic AEs were reported by 24.4% (239 participants) and 53.0% (519 participants), respectively (Table 34).

Most of the solicited local and systemic AEs following vaccination with AZD1222 were mild (Grade 1) to moderate (Grade 2) in severity (Table 34). In the AZD1222 group, solicited local and systemic AEs were reported less frequently within 7 days post second dose (53.4% [977 participants] and 47.3% [862 participants], respectively) than post first dose (68.3% [1250 participants] and 64.7% [1191 participants], respectively). In the AZD1222 and placebo groups, when compared with the first dose, solicited local and systemic AEs reported post second dose were milder and reported less frequently. Of note, 0.2% of participants each in the AZD1222 group (3 participants) and placebo group (2 participants) reported potentially life-threatening (Grade 4) solicited systemic AEs within 7 days after any dose (Table 34). The investigator assessed that none of these events met the criteria for an SAE or MAAE. See Section 9.8.1.3 for additional detail on the e-diary collection of solicited AEs.

Table 34 Overall Summary of Solicited (Local and Systemic) Adverse Events Within 7 Days After Each Dose (Safety Analysis Set)

Adverse Event Category		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Participants with any solicited local or systemic AE, n (%)	Any local and/or systemic, n/Ev (%)	1679/1956 (85.8)	577/981 (58.8)	1513/1854 (81.6)	469/926 (50.6)	1235/1829 (67.5)	366/908 (40.3)
	Mild	783 (40.0)	302 (30.8)	791 (42.7)	281 (30.3)	815 (44.6)	216 (23.8)
	Moderate	748 (38.2)	252 (25.7)	594 (32.0)	173 (18.7)	391 (21.4)	140 (15.4)
	Moderate/Severe [a]	16 (0.8)	1 (0.1)	14 (0.8)	1 (0.1)	3 (0.2)	0
	Severe	127 (6.5)	18 (1.8)	109 (5.9)	11 (1.2)	25 (1.4)	8 (0.9)
	Potentially life-threatening	3 (0.2)	2 (0.2)	3 (0.2)	2 (0.2)	0	0
Participants with any solicited local AE, n (%)	Any local, n/Ev (%)	1440/1944 (74.1)	239/979 (24.4)	1250/1830 (68.3)	173/920 (18.8)	977/1829 (53.4)	120/908 (13.2)
	Mild	1128 (58.0)	221 (22.6)	1014 (55.4)	163 (17.7)	859 (47.0)	111 (12.2)
	Moderate	279 (14.4)	16 (1.6)	207 (11.3)	9 (1.0)	113 (6.2)	8 (0.9)
	Moderate/Severe [a]	22 (1.1)	1 (0.1)	17 (0.9)	1 (0.1)	5 (0.3)	0
	Severe	10 (0.5)	0	10 (0.5)	0	0	0
	Potentially life-threatening	0	0	0	0	0	0

Adverse Event Category		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Participants with any solicited systemic AE, n (%)	Any systemic, n/Ev (%)	1395/1947 (71.6)	519/980 (53.0)	1191/1842 (64.7)	415/924 (44.9)	862/1821 (47.3)	314/905 (34.7)
	Mild	561 (28.8)	247 (25.2)	516 (28.0)	230 (24.9)	490 (26.9)	168 (18.6)
	Moderate	704 (36.2)	251 (25.6)	564 (30.6)	171 (18.5)	345 (18.9)	137 (15.1)
	Severe	124 (6.4)	18 (1.8)	106 (5.8)	11 (1.2)	25 (1.4)	8 (0.9)
	Potentially life-threatening	3 (0.2)	2 (0.2)	3 (0.2)	2 (0.2)	0	0

[a] Intensity categories for erythema and induration only; measurements of ≥ 5.1 cm. See Section 9.9.2 for further details.

Note: If a participant reported more than one occurrence of a solicited AE, the participant was counted once in each type of solicited AE with preference given to the greatest intensity grade.

Note: Percentages were based on the total number of participants evaluated for each solicited AE category.

Note: For participants in the Substudy, solicited AEs collected within 7 days after vaccination (Days 1 to 7) via e-diary were summarized.

Note: Some solicited AEs had a missing severity grade reported.

AE = adverse event; Ev = total number of participants evaluated.

Source: Table 14.3.3.1.1

For an overview of solicited AEs within 7 days of each dose by Substudy subgroups for age at randomization, race, gender (male and female), comorbidity at baseline, and baseline serostatus, see Section 12.2.4.1.

12.2.1.2 Overview of Unsolicited Adverse Events Within 28 Days After Any Dose

For an overall summary of unsolicited AEs within 28 days after any dose (ie, until Day 29 post first dose and Day 57 post second dose), see Table 35. In the SAF, 40.6% of participants (8771 participants) in the AZD1222 group and 29.7% of participants (3201 participants) in the placebo group reported an unsolicited AE within 28 days after any dose. In the AZD1222 group, there were 26.6% of participants (5736 participants) with an unsolicited AE within 28 days of the first dose and 24.4% of participants (5074 participants) within 28 days of the second dose.

The majority of the unsolicited events were mild (Grade 1) to moderate (Grade 2) in severity; the proportion of events with severe or life-threatening (≥ Grade 3) severity was 1.0% (225 participants) in the AZD1222 group and 1.1% (116 participants) in the placebo group after any dose (Table 35). In the AZD1222 group, there were 0.6% of participants (129 participants) with an unsolicited AE ≥ Grade 3 in severity within 28 days of the first dose and 0.5% of participants (98 participants) with an unsolicited AE ≥ Grade 3 in severity within 28 days of the second dose.

A total of 170 participants incorrectly recorded 302 unsolicited AEs (all were nonserious) in the e-diary (start date > 7 days post dose) as solicited AEs, but these events are not expected to impact the overall safety findings. In addition, 172 non-Substudy participants were mistakenly issued e-diaries and recorded solicited AEs in error; the summary of unsolicited AEs within 28 days of each dose will be updated accordingly in the addendum to this CSR. For further detail, see Section 9.9.1.

Related unsolicited AEs, as determined by the investigator, were reported in 28.9% of participants (6238 participants) in the AZD1222 group and 14.1% of participants (1525 participants) in the placebo group following any dose; related AEs were most commonly mild (Grade 1) or moderate (Grade 2) in severity (Table 35).

The incidence of related severe (Grade 3) AEs, as determined by the investigator, was 0.2% of participants (46 participants) in the AZD1222 group and 0.1% of participants (14 participants) in the placebo group after any dose. No participant had a life-threatening (Grade 4) event (Table 35).

The frequency of AEs leading to discontinuation from study intervention or study discontinuation was similar between the AZD1222 and placebo groups (Table 35).

Adverse events reported within 28 days following any dose (SAEs, MAAEs, and AESIs) were balanced between the AZD1222 and placebo groups.

Serious AEs within 28 days after any dose were reported in 0.5% of participants (101 participants) in the AZD1222 group and 0.5% of participants (53 participants) in the placebo group. Over the entire study for the SAF, < 1% of participants reported an SAE (0.6% of participants [140 participants] in the AZD1222 group and 0.7% of participants [78 participants] in the placebo group) (see Section 12.3.3).

One participant each in both the AZD1222 and placebo groups reported a related SAE, within 28 days after any dose, as determined by the investigator (Table 35). Over the entire study for the SAF, 1 participant in the AZD1222 group (2 events) and 2 participants in the placebo group (2 events) reported SAEs that were considered related to study intervention, as determined by the investigator (see Section 12.3.3.1).

Adverse events of special interest within 28 days after any dose occurred in 2.0% of participants (442 participants) in the AZD1222 group and 3.0% of participants (319 participants) in the placebo group (Table 35). Over the entire study for the SAF, 2.4% of participants (525 participants) in the AZD1222 group and 3.9% of participants (416 participants) in the placebo group reported AESIs (see Section 12.2.5).

A total of 15 SAEs with a fatal outcome (8 out of 21587 participants in the AZD1222 group and 7 out of 10792 participants in the placebo group) occurred as of the cut-off date, irrespective of the blinding period (see Table 14.3.2.1.2.7 and Table 14.3.2.2.9). None of the fatal events in either the AZD1222 or placebo groups were considered to be related to study intervention by the investigator.

Medically attended AEs within 28 days after any dose were reported by 6.0% of participants (1288 participants) in the AZD1222 group and 5.9% of participants (632 participants) in the placebo group. Over the entire study for the SAF, 7.5% of participants (1617 participants) in the AZD1222 group and 7.6% of participants (815 participants) in the placebo group reported an MAAE (see Section 12.3.2).

Table 35 Overall Summary of Unsolicited Adverse Events Within 28 Days After Each Dose (Safety Analysis Set)

Adverse Event	Number (%) of participants					
	After any dose		After first dose		After second dose	
	AZD1222 (N = 21587)	Placebo (N = 10792)	AZD1222 (N = 21587)	Placebo (N = 10792)	AZD1222 (N = 20773)	Placebo (N = 9947)
All unsolicited AEs	8771 (40.6)	3201 (29.7)	5736 (26.6)	1926 (17.8)	5074 (24.4)	1797 (18.1)
≥ Grade 3 severity	225 (1.0)	116 (1.1)	129 (0.6)	69 (0.6)	98 (0.5)	47 (0.5)
Serious AEs	101 (0.5)	53 (0.5)	57 (0.3)	36 (0.3)	44 (0.2)	17 (0.2)
Related AEs by severity [a]						
Mild	4994 (23.1)	1291 (12.0)	3033 (14.1)	638 (5.9)	3131 (15.1)	836 (8.4)
Moderate	1198 (5.5)	220 (2.0)	733 (3.4)	91 (0.8)	525 (2.5)	132 (1.3)
Severe	46 (0.2)	14 (0.1)	28 (0.1)	5 (< 0.1)	18 (< 0.1)	9 (< 0.1)
Potentially life-threatening	0	0	0	0	0	0
Fatal	0	0	0	0	0	0
Total	6238 (28.9)	1525 (14.1)	3794 (17.6)	734 (6.8)	3674 (17.7)	977 (9.8)
Related SAEs	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	0	0
AEs leading to discontinuation from study intervention	266 (1.2)	162 (1.5)	266 (1.2)	162 (1.5)	0	0
Related AEs leading to discontinuation from study intervention	22 (0.1)	7 (< 0.1)	22 (0.1)	7 (< 0.1)	0	0

Adverse Event	Number (%) of participants					
	After any dose		After first dose		After second dose	
	AZD1222 (N = 21587)	Placebo (N = 10792)	AZD1222 (N = 21587)	Placebo (N = 10792)	AZD1222 (N = 20773)	Placebo (N = 9947)
AEs leading to study discontinuation	3 (< 0.1)	5 (< 0.1)	2 (< 0.1)	5 (< 0.1)	1 (< 0.1)	0
Related AEs leading to study discontinuation	0	0	0	0	0	0
MAAEs	1288 (6.0)	632 (5.9)	705 (3.3)	365 (3.4)	621 (3.0)	286 (2.9)
AEs with outcome of death	3 (< 0.1)	5 (< 0.1)	2 (< 0.1)	5 (< 0.1)	1 (< 0.1)	0
Related AEs with outcome of death	0	0	0	0	0	0
AESIs	442 (2.0)	319 (3.0)	315 (1.5)	180 (1.7)	130 (0.6)	143 (1.4)
Related AESIs	58 (0.3)	26 (0.2)	41 (0.2)	17 (0.2)	19 (< 0.1)	12 (0.1)

[a] Participants with more than 1 event were counted only once for the maximum severity grade.

Note: Adverse event reporting within 1 to 28 days post any dose were included. Adverse events reported after participant unblinding/authorized COVID-19 vaccine administration were excluded.

Note: Participants with multiple events within a category were counted only once for that category.

Note: Percentages were based on the number of participants in the analysis set by study arm and vaccine received for the period summarized.

Note: Adverse event reporting during the entire period of the study were included. Adverse events were recorded for 28 days post each dose of study intervention. Serious AEs, MAAEs, and AESIs were recorded from the time of signature of the informed consent form through the last participant contact. Adverse events reported after participant unblinding/authorized COVID-19 vaccine administration were excluded.

Note: Related was defined as probably or definitely related, according to the investigator.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; MAAE = medically attended adverse event; SAE = serious adverse event.

Source: Tables 14.3.1.1.1.1 and 14.3.1.3.3.1

For an overview of unsolicited AEs within 28 days of each dose by subgroups for age at randomization, race, gender (male and female), comorbidity at baseline, and baseline serostatus, see Section 12.2.4.2.

12.2.2 Solicited Adverse Events (Substudy) by Category

12.2.2.1 Most Common Solicited Adverse Events

Solicited Local Adverse Events

In the SAF, the most frequently reported solicited local injection site AEs within 7 days after any dose with AZD1222 or placebo were tenderness (68.4% [1326 participants] vs 19.0% [186 participants], respectively) and pain (58.3% [1132 participants] vs 15.7% [154 participants], respectively) (see Table 36). No other solicited local injection site AEs were reported in ≥ 5% of participants in the AZD1222 group. Across all terms, solicited local AEs were reported less frequently post second AZD1222 dose than post first dose in both treatment groups.

Table 36 Summary of Solicited Adverse Events (Local) Within 7 Days After Each Dose (Safety Analysis Set)

Solicited local AEs/ Severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 1962 n (%)	Placebo N = 968 n (%)
Participants with any solicited local AE, n (%)	Total participants evaluated	1944 (95.4)	979 (96.6)	1830 (89.8)	920 (90.8)	1829 (93.2)	908 (93.8)
	None	504 (25.9)	740 (75.6)	580 (31.7)	747 (81.2)	852 (46.6)	788 (86.8)
	Any severity	1440 (74.1)	239 (24.4)	1250 (68.3)	173 (18.8)	977 (53.4)	120 (13.2)
	Mild	1128 (58.0)	221 (22.6)	1014 (55.4)	163 (17.7)	859 (47.0)	111 (12.2)
	Moderate	279 (14.4)	16 (1.6)	207 (11.3)	9 (1.0)	113 (6.2)	8 (0.9)
	Moderate/Severe	22 (1.1)	1 (0.1)	17 (0.9)	1 (0.1)	5 (0.3)	0
	Severe	10 (0.5)	0	10 (0.5)	0	0	0
	Potentially life-threatening	0	0	0	0	0	0

Solicited local AEs/ Severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 1962 n (%)	Placebo N = 968 n (%)
Pain, n (%)	Total participants evaluated	1943 (95.4)	979 (96.6)	1829 (89.8)	919 (90.7)	1829 (93.2)	908 (93.8)
	None	811 (41.7)	825 (84.3)	884 (48.3)	824 (89.7)	1190 (65.1)	825 (90.9)
	Any severity	1132 (58.3)	154 (15.7)	945 (51.7)	95 (10.3)	639 (34.9)	83 (9.1)
	Mild	931 (47.9)	145 (14.8)	796 (43.5)	91 (9.9)	571 (31.2)	78 (8.6)
	Moderate	193 (9.9)	8 (0.8)	140 (7.7)	4 (0.4)	68 (3.7)	4 (0.4)
	Severe	6 (0.3)	0	6 (0.3)	0	0	0
	Potentially life-threatening	0	0	0	0	0	0

Solicited local AEs/ Severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 1962 n (%)	Placebo N = 968 n (%)
Tenderness, n (%)	Total participants evaluated	1938 (95.1)	979 (96.6)	1811 (88.9)	919 (90.7)	1827 (93.1)	907 (93.7)
	None	612 (31.6)	793 (81.0)	683 (37.7)	784 (85.3)	936 (51.2)	816 (90.0)
	Any severity	1326 (68.4)	186 (19.0)	1128 (62.3)	135 (14.7)	891 (48.8)	91 (10.0)
	Mild	1095 (56.5)	174 (17.8)	953 (52.6)	128 (13.9)	807 (44.2)	86 (9.5)
	Moderate	222 (11.5)	12 (1.2)	165 (9.1)	7 (0.8)	84 (4.6)	5 (0.6)
	Severe	9 (0.5)	0	9 (0.5)	0	0	0
	Potentially life-threatening	0	0	0	0	0	0
Erythema/redness, n (%)	Total participants evaluated	1939 (95.2)	979 (96.6)	1811 (88.9)	920 (90.8)	1828 (93.2)	908 (93.8)
	None	1877 (96.8)	973 (99.4)	1767 (97.6)	915 (99.5)	1805 (98.7)	907 (99.9)
	Any severity	62 (3.2)	6 (0.6)	44 (2.4)	5 (0.5)	23 (1.3)	1 (0.1)
	Mild (2.5-5 cm)	42 (2.2)	5 (0.5)	29 (1.6)	4 (0.4)	18 (1.0)	1 (0.1)
	Moderate (5.1-6 cm)	8 (0.4)	0	6 (0.3)	0	2 (0.1)	0
	Moderate/Severe (> 6 cm)	12 (0.6)	1 (0.1)	9 (0.5)	1 (0.1)	3 (0.2)	0

Solicited local AEs/ Severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 2037 n (%)	Placebo N = 1013 n (%)	AZD1222 N = 1962 n (%)	Placebo N = 968 n (%)
Induration/swelling, n (%)	Total participants evaluated	1938 (95.1)	978 (96.5)	1812 (89.0)	918 (90.6)	1824 (93.0)	907 (93.7)
	None	1875 (96.7)	977 (99.9)	1763 (97.3)	917 (99.9)	1798 (98.6)	907 (100.0)
	Any severity	63 (3.3)	1 (0.1)	49 (2.7)	1 (0.1)	26 (1.4)	0
	Mild (2.5-5 cm)	39 (2.0)	1 (0.1)	31 (1.7)	1 (0.1)	18 (1.0)	0
	Moderate (5.1-6 cm)	10 (0.5)	0	6 (0.3)	0	6 (0.3)	0
	Moderate/Severe (> 6 cm)	14 (0.7)	0	12 (0.7)	0	2 (0.1)	0

Note: n was the number of participants providing a response in the e-diary.

Note: All percentages were based on 'n' except for the percentage for 'n', which was based on the number of participants in the analysis set by study arm and dose received for the period summarized.

Note: Intensity categories for erythema and swelling were defined as follows: Mild: 2.5 to 5 cm, Moderate: 5.1 to 10 cm, Severe: > 10 cm, Any: ≥ 2.5 cm, None: < 2.5 cm. Due to limitations in the e-diary, the maximum measurement possible to be recorded was "> 6 cm". Hence, results "> 6 cm" were displayed in the combined category "Moderate/Severe". Life-threatening events were captured as SAEs and reported in SAE tables.

Note: If a participant reported more than one occurrence of the same event, then the event of greatest intensity was included in the analysis.

Note: For participants in the Substudy, solicited AEs collected within 7 days after dosing (Days 1 to 7) via e-diary were summarized.

Note: Some solicited AEs had a missing severity grade reported.

AE = adverse event; SAE = serious adverse event.

Source: Table 14.3.3.2.1

Solicited Systemic Adverse Events

In the SAF, solicited systemic AEs were reported by 71.6% of participants (1395 participants) in the AZD1222 group and 53.0% (519 participants) in the placebo group following any dose (see Table 37). Although solicited systemic AEs were reported at a higher proportion in the AZD1222 group, the events were generally mild or moderate in severity and of short duration (most resolved within 3 days). The most frequently reported solicited systemic AEs within 7 days after either dose with AZD1222 were headache (50.2% [974 participants] vs 35.5% [346 participants] in placebo) and fatigue (49.7% [963 participants] vs 31.2% [305 participants] in placebo); other frequently reported systemic solicited AEs were muscle pain (41.9% [813 participants] vs 19.5% [190 participants] in placebo) and malaise (35.0% [676 participants] vs 17.0% [166 participants] in placebo) (see Table 37).

Table 37 Summary of Solicited Adverse Events (Systemic) Within 7 Days After Each Dose (Safety Analysis Set)

Solicited systemic AEs/severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Participants with any solicited systemic AE, n (%)	Total participants evaluated	1947 (95.6)	980 (96.7)	1842 (90.4)	924 (91.2)	1821 (92.8)	905 (93.5)
	None	552 (28.4)	461 (47.0)	651 (35.3)	509 (55.1)	959 (52.7)	591 (65.3)
	Any systemic AE	1395 (71.6)	519 (53.0)	1191 (64.7)	415 (44.9)	862 (47.3)	314 (34.7)
	Mild	561 (28.8)	247 (25.2)	516 (28.0)	230 (24.9)	490 (26.9)	168 (18.6)
	Moderate	704 (36.2)	251 (25.6)	564 (30.6)	171 (18.5)	345 (18.9)	137 (15.1)
	Severe	124 (6.4)	18 (1.8)	106 (5.8)	11 (1.2)	25 (1.4)	8 (0.9)
	Potentially life-threatening	3 (0.2)	2 (0.2)	3 (0.2)	2 (0.2)	0	0
Fever, n (%)	Total participants evaluated	1935 (95.0)	978 (96.5)	1814 (89.1)	918 (90.6)	1821 (92.8)	905 (93.5)
	None (≤ 37.8°C)	1799 (93.0)	972 (99.4)	1688 (93.1)	912 (99.3)	1808 (99.3)	904 (99.9)
	Any (> 37.8°C)	136 (7.0)	6 (0.6)	126 (6.9)	6 (0.7)	13 (0.7)	1 (0.1)
	37.9°C to 38.4°C	95 (4.9)	2 (0.2)	89 (4.9)	2 (0.2)	9 (0.5)	1 (0.1)
	38.5°C to 38.9°C	31 (1.6)	2 (0.2)	29 (1.6)	2 (0.2)	2 (0.1)	0
	39.0°C to 40.0°C	10 (0.5)	1 (0.1)	8 (0.4)	1 (0.1)	2 (0.1)	0
	≥ 40.1°C	0	1 (0.1)	0	1 (0.1)	0	0

Solicited systemic AEs/severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Chills, n (%)	Total participants evaluated	1939 (95.2)	978 (96.5)	1817 (89.2)	918 (90.6)	1821 (92.8)	905 (93.5)
	None	1393 (71.8)	885 (90.5)	1363 (75.0)	864 (94.1)	1657 (91.0)	849 (93.8)
	Any severity	546 (28.2)	93 (9.5)	454 (25.0)	54 (5.9)	164 (9.0)	56 (6.2)
	Mild	492 (25.4)	91 (9.3)	401 (22.1)	52 (5.7)	161 (8.8)	56 (6.2)
	Moderate	6 (0.3)	0	6 (0.3)	0	0	0
	Severe	45 (2.3)	2 (0.2)	44 (2.4)	2 (0.2)	3 (0.2)	0
	Potentially life-threatening	3 (0.2)	0	3 (0.2)	0	0	0
Muscle pain, n (%)	Total participants evaluated	1939 (95.2)	976 (96.3)	1821 (89.4)	918 (90.6)	1820 (92.8)	904 (93.4)
	None	1126 (58.1)	786 (80.5)	1149 (63.1)	786 (85.6)	1482 (81.4)	805 (89.0)
	Any severity	813 (41.9)	190 (19.5)	672 (36.9)	132 (14.4)	338 (18.6)	99 (11.0)
	Mild	444 (22.9)	126 (12.9)	363 (19.9)	97 (10.6)	237 (13.0)	66 (7.3)
	Moderate	329 (17.0)	60 (6.1)	272 (14.9)	31 (3.4)	98 (5.4)	32 (3.5)
	Severe	38 (2.0)	2 (0.2)	35 (1.9)	2 (0.2)	3 (0.2)	1 (0.1)
	Potentially life-threatening	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)	0	0

Solicited systemic AEs/severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Fatigue, n (%)	Total participants evaluated	1936 (95.0)	977 (96.4)	1817 (89.2)	920 (90.8)	1820 (92.8)	903 (93.3)
	None	973 (50.3)	672 (68.8)	1020 (56.1)	699 (76.0)	1330 (73.1)	739 (81.8)
	Any severity	963 (49.7)	305 (31.2)	797 (43.9)	221 (24.0)	490 (26.9)	164 (18.2)
	Mild	389 (20.1)	135 (13.8)	334 (18.4)	106 (11.5)	270 (14.8)	79 (8.7)
	Moderate	499 (25.8)	159 (16.3)	397 (21.8)	110 (12.0)	208 (11.4)	78 (8.6)
	Severe	72 (3.7)	10 (1.0)	63 (3.5)	4 (0.4)	12 (0.7)	6 (0.7)
	Potentially life-threatening	2 (0.1)	0	2 (0.1)	0	0	0
Headache, n (%)	Total participants evaluated	1942 (95.3)	975 (96.2)	1829 (89.8)	921 (90.9)	1820 (92.8)	901 (93.1)
	None	968 (49.8)	629 (64.5)	1055 (57.7)	656 (71.2)	1299 (71.4)	728 (80.8)
	Any severity	974 (50.2)	346 (35.5)	774 (42.3)	265 (28.8)	521 (28.6)	173 (19.2)
	Mild	537 (27.7)	227 (23.3)	441 (24.1)	191 (20.7)	346 (19.0)	115 (12.8)
	Moderate	405 (20.9)	111 (11.4)	308 (16.8)	69 (7.5)	166 (9.1)	55 (6.1)
	Severe	30 (1.5)	8 (0.8)	23 (1.3)	5 (0.5)	8 (0.4)	3 (0.3)
	Potentially life-threatening	1 (< 0.1)	0	1 (< 0.1)	0	0	0

Solicited systemic AEs/severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Malaise, n (%)	Total participants evaluated	1934 (94.9)	974 (96.2)	1811 (88.9)	917 (90.5)	1820 (92.8)	901 (93.1)
	None	1258 (65.0)	808 (83.0)	1268 (70.0)	805 (87.8)	1529 (84.0)	817 (90.7)
	Any severity	676 (35.0)	166 (17.0)	543 (30.0)	112 (12.2)	291 (16.0)	84 (9.3)
	Mild	341 (17.6)	97 (10.0)	278 (15.4)	68 (7.4)	181 (9.9)	51 (5.7)
	Moderate	287 (14.8)	67 (6.9)	227 (12.5)	42 (4.6)	99 (5.4)	33 (3.7)
	Severe	45 (2.3)	2 (0.2)	36 (2.0)	2 (0.2)	10 (0.5)	0
	Potentially life-threatening	2 (0.1)	0	2 (0.1)	0	0	0
Nausea, n (%)	Total participants evaluated	1933 (94.9)	974 (96.2)	1811 (88.9)	917 (90.5)	1820 (92.8)	901 (93.1)
	None	1638 (84.7)	856 (87.9)	1604 (88.6)	846 (92.3)	1681 (92.4)	838 (93.0)
	Any severity	295 (15.3)	118 (12.1)	207 (11.4)	71 (7.7)	139 (7.6)	63 (7.0)
	Mild	218 (11.3)	81 (8.3)	153 (8.4)	52 (5.7)	114 (6.3)	43 (4.8)
	Moderate	76 (3.9)	36 (3.7)	53 (2.9)	18 (2.0)	25 (1.4)	20 (2.2)
	Severe	0	1 (0.1)	0	1 (0.1)	0	0
	Potentially life-threatening	0	0	0	0	0	0

Solicited systemic AEs/severity		Days 1 to 7 after any dose		Days 1 to 7 after first dose		Days 1 to 7 after second dose	
		AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 2037)	Placebo (N = 1013)	AZD1222 (N = 1962)	Placebo (N = 968)
Vomiting, n (%)	Total participants evaluated	1933 (94.9)	974 (96.2)	1809 (88.8)	917 (90.5)	1820 (92.8)	901 (93.1)
	None	1899 (98.2)	956 (98.2)	1787 (98.8)	906 (98.8)	1806 (99.2)	894 (99.2)
	Any severity	34 (1.8)	18 (1.8)	22 (1.2)	11 (1.2)	14 (0.8)	7 (0.8)
	Mild	20 (1.0)	16 (1.6)	12 (0.7)	10 (1.1)	10 (0.5)	6 (0.7)
	Moderate	14 (0.7)	2 (0.2)	10 (0.6)	1 (0.1)	4 (0.2)	1 (0.1)
	Severe	0	0	0	0	0	0
	Potentially life-threatening	0	0	0	0	0	0

Note: n was the number of participants providing a response in the e-diary.

Note: All percentages were based on 'n' except for the percentage for 'n', which was based on the number of participants in the analysis set by study arm and dose received for the period summarized.

Note: If a participant reported more than one occurrence of the same event, then the event of greatest intensity was included in the analysis. For fever, participants were counted based on the highest temperature recorded by the participant diary within 7 days after dosing.

Note: For participants in the Substudy, solicited AEs collected within 7 days after dosing (Days 1 to 7) via the e-diary were summarized.

Note: Some solicited AEs had a missing severity grade reported.

AE = adverse event.

Source: Table 14.3.3.3.1

12.2.2.2 Solicited Adverse Events by Intensity

Severity was assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in the CSP Appendix D; for additional detail, see Section 9.8.1.3. Because solicited AEs were expected to occur after dosing, they were not assessed for relationship to study intervention.

For a summary of solicited local AEs by severity for the SAF, see Table 36. Few participants reported severe solicited local AEs for any specific term, and smaller percentages of participants reported severe events following the second dose. No severe solicited local AEs were reported in ≥ 1% of participants after any AZD1222 dose. No life-threatening events were reported.

Overall, solicited local AEs were of short duration; the median number of days with solicited local AEs within 7 days in the AZD1222 group post first dose was 2.0 days for pain, 3.0 days for tenderness, 2.0 days for erythema/redness, and 2.0 days for induration/swelling (see Table 14.3.3.7.1). A shorter duration was observed for the median number of days with solicited local AEs within 7 days post second dose.

The majority of solicited systemic AEs in the AZD1222 group were mild and moderate in severity. Few severe solicited systemic AEs were reported for any specific term. Solicited systemic AEs with ≥ Grade 3 severity after any dose with AZD1222 were reported in < 1% of participants across all terms.

Solicited systemic AEs were reported less frequently post second dose than post first dose of AZD1222. In general, smaller percentages of participants reported severe events following the second dose (see Table 37).

Overall, solicited systemic AEs were of short duration; the median number of days with solicited systemic AEs within 7 days post first dose was 1.0 day each for fatigue, headache, muscle pain, malaise, nausea, vomiting, chills, and fever (see Table 14.3.3.8.1). A similar duration was observed for median number of days with solicited local AEs within 7 days post second dose.

12.2.3 Adverse Events by System Organ Class and Preferred Term

12.2.3.1 Most Common Unsolicited Adverse Events Within 28 Days Post Dose

For a summary of unsolicited AEs for the SAF within 28 days after any dose, see Table 14.3.2.5.1. For an overall summary of unsolicited AEs by SOC and PT for the SAF within 28 days following any dose, see Table 14.3.1.2.1. For unsolicited AEs with an incidence ≥ 1% reported within 28 days after any dose and over the entire study for the SAF, see Table 14.3.2.5.1. For an overall summary of unsolicited AEs by SOC and PT for the SAF

within 28 days following any dose, see Table 14.3.1.2.1. For unsolicited AEs with an incidence ≥ 1% reported within 28 days after dosing and over the entire study for the SAF, see Table 38.

The SOC in which the highest proportion of participants reported unsolicited AEs within 28 days following any dose in the AZD1222 and placebo groups was General disorders and administration site conditions (21.6% [4654 participants] vs 9.4% [1016 participants]); all other SOCs had a frequency below 10% in the AZD1222 group (see Table 14.3.1.2.1).

The most common AE reported in the SOC of Nervous system disorders was headache; 6.2% (1346 participants) in the AZD1222 group and 4.6% (498 participants) in the placebo group (see Table 14.3.1.2.1). The majority of the events of headache were considered related by the investigator, and headache was one of the most frequently reported solicited systemic AEs (see Table 37). The other PTs reported in this SOC with a frequency > 0.1% in the AZD1222 and placebo groups, respectively, included dizziness (0.8% [164 participants] vs 0.7% [74 participants]), and paraesthesia (0.3% [58 participants] vs 0.3% [27 participants]).

For participants in the SAF, the most common unsolicited AEs were consistent with AEs commonly observed following vaccination (see Table 38). The most frequently reported unsolicited AEs in the AZD1222 group were pain, headache, injection site pain, fatigue, and body temperature increased; all of which were reported at a higher frequency in the AZD1222 group compared with the placebo group. These events were consistent with AEs commonly observed following vaccination. Other unsolicited AEs were reported in < 3.0% of participants in the AZD1222 group.

Table 38 Unsolicited Adverse Events within 28 Days Following Dosing (≥ 1% in Either Treatment Group) by PT (Safety Analysis Set)

MedDRA version 23.1 PT	Number (%) of participants After any dose	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Within 28 days after any dose	8771 (40.6)	3201 (29.7)
Pain	1766 (8.2)	249 (2.3)
Injection site pain	1473 (6.8)	217 (2.0)
Headache	1346 (6.2)	498 (4.6)
Fatigue	1102 (5.1)	383 (3.5)
Body temperature increased	741 (3.4)	92 (0.9)
Diarrhoea	541 (2.5)	233 (2.2)
Rhinorrhoea	487 (2.3)	250 (2.3)
Myalgia	441 (2.0)	119 (1.1)
Chills	435 (2.0)	104 (1.0)
Oropharyngeal pain	425 (2.0)	235 (2.2)
Nasal congestion	347 (1.6)	215 (2.0)
Cough	340 (1.6)	188 (1.7)
Injection related reaction	328 (1.5)	66 (0.6)
Pain in extremity	301 (1.4)	75 (0.7)
COVID-19	295 (1.4)	264 (2.4)
Reactogenicity event	282 (1.3)	45 (0.4)
Nausea	250 (1.2)	98 (0.9)
Arthralgia	247 (1.1)	61 (0.6)

Note: Most frequent AEs were reported by > 1% participants in any study arm group.

Note: Adverse events reporting within 1 to 28 days post any dose were included. Adverse events reported after participant unblinding/ authorized COVID-19 vaccine administration were excluded.

Note: AEs were sorted by decreasing order of total frequency in PT.

Note: Participants with more than one event within a PT were counted only once for that PT.

Note: Percentages were based on the number of participants in the analysis set by study arm and vaccine received for the period summarized.

AE = adverse event; COVID-19 = coronavirus disease-2019; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

Source: Table 14.3.2.5.1

12.2.3.2 Unsolicited Adverse Events by Intensity

In the SAF, the majority of unsolicited AEs were mild to moderate in severity (see Table 14.3.1.3.1).

A greater proportion of participants in the AZD1222 group reported mild and moderate events (28.2% [6086 participants] and 11.4% [2458 participants], respectively) compared with the placebo group (19.9% [2151 participants] and 8.6% [933 participants], respectively). This difference was primarily driven by AEs reflective of reactogenicity and included pain (mild events reported in 6.3% [1353 participants] in the AZD1222 group and 1.8% [193 participants] in the placebo group; moderate events reported in 1.9% [407 participants] in the AZD1222 group and 0.5% [53 participants] in the placebo group), injection site pain (mild events reported in 6.4% [1380 participants] in the AZD1222 group and 1.9% [208 participants] in the placebo group; moderate events reported in 0.4% [92 participants] in the AZD1222 group and < 0.1% [9 participants] in the placebo group), and fatigue (mild events reported in 4.5% [969 participants] in the AZD1222 group and 3.0% [324 participants] in the placebo group; moderate events reported in 0.6% [122 participants] in the AZD1222 group and 0.5% [54 participants] in the placebo group).

Few participants in either the AZD1222 or placebo group reported severe, potentially life-threatening, or fatal events; there were no imbalances by SOC or PT between the AZD1222 and placebo group for these events.

12.2.4 Subgroup Analyses

In the SAF, selected AE parameters were also reviewed by subgroup for age at randomization, race, gender (male and female), comorbidity at baseline, and baseline serostatus using the SAF (see Section 9.8.2.1 and Table 13 for additional detail).

12.2.4.1 Solicited Adverse Events (Substudy)

Effect of Age

For an overview of solicited AEs within 7 days of each dose by substudy age group, see Table 14.3.3.1.3. With respect to the reactogenicity profile of AZD1222 by age group, solicited local and systemic AEs were milder and reported less frequently in older adults (≥ 65 years) compared with younger adults (18 to 64 years). Solicited AEs were milder and reported less frequently post second dose than post first dose in both age groups (see Tables 14.3.3.1.4, 14.3.3.2.4, and 14.3.3.3.4). Solicited AEs (local and systemic) were of short duration (most completely resolved within 3 days) in both age subgroups (see Tables 14.3.3.7.4 and 14.3.3.8.4).

Effect of Gender

With respect to the reactogenicity profile of AZD1222 by gender, in general, female participants reported a higher incidence of solicited AEs (local and systemic) compared with

male participants following the first or second dose. Solicited local and systemic AEs were milder and reported less frequently post second dose compared with the first dose in both male and female participants (see Table 14.3.3.1.5). A similar pattern was observed in the placebo group.

Comorbidity as a Risk Factor

With respect to the reactogenicity profile of AZD1222 by age group, the incidence of related solicited local and systemic AEs, as determined by the investigator, were similar in participants with and without a comorbidity at baseline (see Table 14.3.3.1.8). Solicited AEs were milder and reported less frequently post second dose than post first dose, regardless of whether participants had a comorbidity at baseline (see Table 14.3.3.1.7).

Effect of Serostatus

Overall, 95.4% of participants (30889 participants) were seronegative at baseline (see Table 14.1.4.1). Based on the limited data in participants who were seropositive (623 participants in the AZD1222 group and 292 participants in the placebo group), there were no clinically meaningful imbalances in the reactogenicity profile for solicited AEs between subgroups by serostatus at baseline (see Table 14.3.3.1.2). In participants who were seropositive or seronegative at baseline, solicited AEs (local and systemic) were of short duration (most resolved within 2 days) (see Tables 14.3.3.7.2 and 14.3.3.8.2).

12.2.4.2 Unsolicited Adverse Events (Overall Study)

Effect of Age

Overall, the safety profile of AZD1222 was generally similar in older adults compared with younger adults 18 to 64 years of age, with older adults reporting reduced reactogenicity (see Table 14.3.1.1.1.3). The incidence of unsolicited AEs reported within 28 days of any AZD1222 dose was lower in the in older adults ≥ 65 years of age (33.4% [1612 participants]) compared with younger adults 18 to 64 years of age (42.7% [7159 participants]). The majority of unsolicited AEs were mild to moderate in severity; the incidence of severe unsolicited AEs reported within 28 days after any AZD1222 dose was low in both the older adults (0.1% [7 participants]) and younger adults 18 to 64 years of age (0.2% [39 participants]) subgroups. A similar pattern was observed in the placebo group.

Effect of Gender

The incidence of unsolicited AEs reported within 28 days of any AZD1222 dose was lower in male participants (37.9% [4551 participants]) compared with female participants (44.1% [4220 participants]) (see Table 14.3.1.1.1.4). The majority of unsolicited AEs were mild to moderate in severity; the incidence of severe unsolicited AEs reported within 28 days after any AZD1222 dose was low in both male participants (0.2% [19 participants]) and female participants (0.3% [27 participants]). A similar pattern was observed in the placebo group.

Comorbidity as a Risk Factor

The incidence of unsolicited AEs reported within 28 days of any AZD1222 dose was similar in participants with no comorbidity at baseline (41.7% [3681 participants]) compared with participants with a comorbidity at baseline (39.9% [5088 participants]). The majority of unsolicited AEs were mild to moderate in severity; the incidence of severe unsolicited AEs reported within 28 days after any AZD1222 vaccination was low in both comorbidity subgroups (0.2% [24 participants] vs 0.2% [22 participants] with and without a comorbidity at baseline, respectively) (see Table 14.3.1.1.1.6). A similar pattern was observed in the placebo group.

Effect of Serostatus

The incidence of unsolicited AEs reported within 28 days of any AZD1222 vaccination for participants who were seronegative or seropositive at baseline was 40.8% (8412 participants) and 34.2% (213 participants), respectively. The majority of unsolicited AEs were mild to moderate in severity; the incidence of severe unsolicited AEs reported within 28 days after any AZD1222 vaccination was 0.2% (45 participants) for seronegative participants and 0.2% (1 participant) for seropositive participants (see Table 14.3.1.1.1.2). A similar pattern was observed in the placebo group.

12.2.5 Adverse Events of Special Interest

For AESIs for the SAF, see Table 14.3.2.6.1.

Pre-defined lists of the AESIs for AZD1222 included neurologic, vascular, haematologic, and immunologic events. The AESI groupings were predetermined in response to formal feedback from the FDA. For a list of AESIs for AZD1222, see Appendix 7 in the SAP. For narratives of all AESIs (Grade 2 and higher) and all related AESIs of Grade 1, see Appendix 16.2.7.1.

Events reported post-unblinding were not included in the overall summary tables but are referenced in the relevant sections below for completeness. For a summary of AESIs and related AESIs by category, PT, and blinding period, see Tables 14.3.2.6.2.7 and 14.3.2.6.4.7, respectively. For a summary of PIMC by PT and blinding period, see Table 14.3.2.15.2.7.

Overall, in the SAF, the incidence of AESI was low (2.4% of participants [525 participants] in the AZD1222 group and 3.9% of participants [416 participants] in the placebo group (see Table 14.3.2.6.1). For all AESIs, there were no clinically meaningful imbalances in the incidence of AESIs by category or PT. There were 3 fatal events categorized as AESIs reported in the placebo group (2 participants reported the PT of COVID-19 pneumonia and 1 participant reported the PT of hemorrhagic transformation stroke) and 0 fatal events reported in the AZD1222 group (see Table 14.3.2.1.5). For reports of PTs from the pre-defined AESI categories, see Table 39. Neurologic and/or neuroinflammatory AESIs were reported by 0.6% of participants (121 participants) in the AZD1222 group and 0.4% of participants

(48 participants) in the placebo group. Additional details for these AESIs are provided in Section 12.2.5.1.

Table 39 Adverse Events of Special Interest by Category and PT (Safety Analysis Set)

MedDRA version 23.1 Category Sub-category Preferred Term	Number (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Participants with ≥ 1 AESI	525 (2.4) / 0.11	416 (3.9) / 0.18
Participants with any neurologic and/or neuroinflammatory AESI	121 (0.6) / 0.03	48 (0.4) / 0.02
Neurologic [a]	114 (0.5) / 0.02	48 (0.4) / 0.02
Chronic inflammatory demyelinating polyradiculoneuropathy [b]	1 (<0.1) / <0.01	0
Dysaesthesia	0	4 (<0.1) / <0.01
Epilepsy	1 (<0.1) / <0.01	0
Guillain-Barre syndrome [b]	1 (<0.1) / <0.01	0
Hyperaesthesia	3 (<0.1) / <0.01	0
Hypoaesthesia	31 (0.1) / <0.01	10 (<0.1) / <0.01
Muscular weakness	10 (<0.1) / <0.01	1 (<0.1) / <0.01
Neuralgia	2 (<0.1) / <0.01	3 (<0.1) / <0.01
Neuritis	2 (<0.1) / <0.01	2 (<0.1) / <0.01
Neuropathy peripheral	5 (<0.1) / <0.01	2 (<0.1) / <0.01
Paraesthesia	61 (0.3) / 0.01	27 (0.3) / 0.01
Peripheral sensory neuropathy	1 (<0.1) / <0.01	0
Polyneuropathy	0	1 (<0.1) / <0.01
Seizure	2 (<0.1) / <0.01	1 (<0.1) / <0.01
Sensory disturbance	1 (<0.1) / <0.01	1 (<0.1) / <0.01
Sensory loss	0	1 (<0.1) / <0.01
Visual impairment	2 (<0.1) / <0.01	0

MedDRA version 23.1 Category Sub-category Preferred Term	Number (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Potential Immune Mediated Conditions (PIMC)	**393 (1.8) / 0.08**	**366 (3.4) / 0.16**
PIMC - Gastrointestinal disorders	1 (<0.1) / <0.01	1 (<0.1) / <0.01
Colitis ulcerative	1 (<0.1) / <0.01	1 (<0.1) / <0.01
PIMC - Metabolic disorders	2 (<0.1) / <0.01	1 (<0.1) / <0.01
Autoimmune thyroiditis	1 (<0.1) / <0.01	1 (<0.1) / <0.01
Basedow's disease	1 (<0.1) / <0.01	0
PIMC - Musculoskeletal disorders	3 (<0.1) / <0.01	0
Polymyalgia rheumatica	1 (<0.1) / <0.01	0
Rheumatoid arthritis	2 (<0.1) / <0.01	0
PIMC – Neuroinflammatory disorders [a]	8 (<0.1) / <0.01	1 (<0.1) / <0.01
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (<0.1) / <0.01	0
Facial paralysis	5 (<0.1) / <0.01	0
Guillain-Barre syndrome	1 (<0.1) / <0.01	0
Narcolepsy	1 (<0.1) / <0.01	0
Polyneuropathy	0	1 (<0.1) / <0.01
VIth nerve paralysis	1 (<0.1) / <0.01	0
PIMC - Others	2 (<0.1) / <0.01	1 (<0.1) / <0.01
Immune thrombocytopenia	0	1 (<0.1) / <0.01
Raynaud's phenomenon	2 (<0.1) / <0.01	0
PIMC - Skin disorders	3 (<0.1) / <0.01	0
Psoriasis	2 (<0.1) / <0.01	0
Rosacea	1 (<0.1) / <0.01	0

MedDRA version 23.1 Category Sub-category Preferred Term	Number (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
PIMC – VAERD	374 (1.7) / 0.08	362 (3.4) / 0.16
Acute respiratory distress syndrome	1 (<0.1) / <0.01	0
COVID-19	368 (1.7) / 0.08	354 (3.3) / 0.16
COVID-19 pneumonia	6 (<0.1) / <0.01	17 (0.2) / <0.01
Pneumonitis	1 (<0.1) / <0.01	0
Suspected COVID-19	1 (<0.1) / <0.01	1 (<0.1) / <0.01
Vascular	23 (0.1) / <0.01	9 (<0.1) / <0.01
Acute myocardial infarction	3 (<0.1) / <0.01	1 (<0.1) / <0.01
Cardiac ventricular thrombosis	0	1 (<0.1) / <0.01
Cerebral artery occlusion	0	1 (<0.1) / <0.01
Cerebrovascular accident	1 (<0.1) / <0.01	0
Coronary artery occlusion	1 (<0.1) / <0.01	0
Deep vein thrombosis	6 (<0.1) / <0.01	3 (<0.1) / <0.01
Haemorrhagic transformation stroke	0	1 (<0.1) / <0.01
Ischaemic stroke	4 (<0.1) / <0.01	1 (<0.1) / <0.01
Myocardial infarction	2 (<0.1) / <0.01	2 (<0.1) / <0.01
Peripheral artery occlusion	1 (<0.1) / <0.01	0
Pulmonary embolism	2 (<0.1) / <0.01	1 (<0.1) / <0.01
Retinal vein occlusion	1 (<0.1) / <0.01	0
Thrombosis	1 (<0.1) / <0.01	0
Transient ischaemic attack	2 (<0.1) / <0.01	1 (<0.1) / <0.01
Hematologic	2 (<0.1) / <0.01	1 (<0.1) / <0.01
Thrombocytopenia	2 (<0.1) / <0.01	0
Immune thrombocytopenia	0	1 (<0.1) / <0.01

[a] The PTs in this category were included in the neurologic and PIMC category of neuroinflammatory events.

[b] The PTs of chronic inflammatory demyelinating polyradiculoneuropathy and Guillain Barre syndrome were reported in the same study participant.

Note: Exposure-adjusted rate (Adj. Rate) was calculated as number of participants with AESIs/total patient-years of observation. Patient-years were determined by summing the total number of follow-up days of each participant in the study arm, and then dividing by 365.25. The exposure period was calculated from time of first intervention to end of study.

Note: Adverse events of special interest were recorded from Day 1 through the last participant contact. AEs reported after participant unblinding/authorized COVID-19 vaccine administration were excluded.

Note: Adverse events were sorted alphabetically by category, and within each category, PTs were sorted by decreasing order of total frequency.

Note: Participants with more than one event within a PT were counted only once for that PT. For PTs that were included in multiple AESI categories or sub-categories, participants were counted once in each category/sub-category for that PT.

Note: Percentages were based on the number of participants in the analysis set by study arm.

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease-2019; MedDRA = Medical Dictionary for Regulatory Activities; PIMC = potentially-immune mediated condition; PT = preferred term; VAERD = vaccine-associated enhanced respiratory disease.

Source: Table 14.3.2.6.1

12.2.5.1 Neurological Events

In the pre-defined list of the AESI category "Neurologic," the proportion of participants who reported neurological AESIs was similar between the AZD1222 (0.5% [114 participants]) and placebo groups (0.4% [48 participants]). In addition, 9 participants in the AZD1222 group and 3 participants in the placebo group reported events in the Neurologic category post unblinding/authorized COVID-19 vaccine administration and were not included in the double-blind period (see Table 14.3.2.6.2.7).

During the double-blind period, the most frequently reported PTs within the category of neurologic events (≥ 5 participants in the AZD1222 group) were paraesthesia (0.3% [61 participants] in the AZD1222 group and 0.3% [27 participants] in the placebo group), hypoaesthesia (0.1% [31 participants] in the AZD1222 group and < 0.1% [10 participants] in the placebo group), and muscular weakness (< 0.1% [10 participants] in the AZD1222 group and < 0.1% [1 participant] in the placebo group) (see Table 14.3.2.6.1). Individual neurologic events are further detailed in the description of the AESI "PIMC - Neuroinflammatory Disorders."

12.2.5.2 Potential Immune-mediated Conditions

In the pre-defined list of the AESI "PIMC," the proportion of participants who reported PIMC AESIs was the lower in the AZD1222 group (1.8% [393 participants]) compared with the placebo group (3.4% [366 participants]) (see Table 14.3.2.6.1). Several subcategories of AESIs were evaluated within the category of PIMC: VAERD, Neuroinflammatory disorders, Gastrointestinal disorders, Metabolic disorders, Musculoskeletal disorders, Skin disorders, Anaphylaxis, and Other disorders. The most commonly reported subcategories of PIMC were VAERD and Neuroinflammatory disorders, which are further described below. The most frequently reported PT within the category of PIMC was COVID-19 (in the VAERD

subcategory) for both the AZD1222 (1.7% [368 participants] and placebo groups (3.3% [354 participants]). With the exception of VAERD as described previously, across all subcategories, no clinically relevant differences were observed between the AZD1222 and placebo groups.

PIMC - Neuroinflammatory Disorders

In the pre-defined list of the AESI "PIMC – Neuroinflammatory Disorders," neuroinflammatory disorders were reported by < 0.1% of participants each in both the AZD1222 and placebo groups (8 and 1 participants, respectively) (see Table 14.3.2.6.1). The most frequently reported PT was facial paralysis, which was reported by 5 participants in the AZD1222 group and 0 participants in the placebo group. These events were nonserious AEs and are further described below.

One participant reported potential immune-mediated neurological (demyelinating) conditions (see Table 14.3.2.6.1). The PTs reported by this participant in the AZD1222 group were chronic inflammatory demyelinating polyradiculoneuropathy and Guillain-Barre syndrome. A more detailed case description is provided below. See Appendix 16.2.7.1 for full narratives for these events.

PPD

The PT of facial paralysis was reported in a total of 5 participants in the AZD1222 group and 0 participants in placebo group. Of the 5 participants in the AZD1222 group, 2 participants

reported facial paralysis after receiving the first dose of study intervention, while 3 participants reported Bell's palsy post second dose (data on file). Brief narratives of these 5 participants are provided below.

PPD

PPD
PPD

One AESI of VIth nerve paralysis was reported in the AZD1222 group:

PPD

PIMC – Anaphylaxis

In the pre-defined list of the AESI "PIMC – Anaphylaxis," which was based on the SMQ (narrow scope) Anaphylactic reactions, no events were reported (see Table 14.3.1.2.1).

PIMC - Vaccine Associated Enhanced Respiratory Disease

In the pre-defined list of the AESI "PIMC – VAERD," there was no evidence of an association between AZD1222 and VAERD. In addition, 21 participants in the AZD1222 group and 28 participants in the placebo group reported events in the PIMC-VAERD category post unblinding/authorized COVID-19 vaccine administration and were not included in the double-blind period (see Table 14.3.2.6.2.7).

During the double-blind period, events in this category were reported by a numerically lower percentage of participants in the AZD1222 group (1.7% [374 participants]) compared with the placebo group (3.4% [362 participants]) (Table 39). The most frequently reported PT was COVID-19 in both the AZD1222 (1.7% [368 participants] and placebo (3.3% [354 participants]) groups, followed by COVID-19 pneumonia which was reported by <0.1% (6 participants) in the AZD1222 group and 0.2% (17 participants) in the placebo group.

12.2.5.3 Vascular Events

In the pre-defined list of the AESI "Vascular," few events were reported (0.1% [23 participants] in the AZD1222 group and < 0.1% [9 participants] in the placebo group); no imbalance between the AZD1222 vs placebo groups was observed in this AESI category. In addition, 4 participants in the AZD1222 group and 5 participants in the placebo group reported events in the Vascular category post unblinding/authorized COVID-19 vaccine administration and were not included in the double-blind period (see Table 14.3.2.6.2.7).

During the double-blind period, the most frequently reported PT (≥ 5 participants in the AZD1222 group) within the category of vascular events was deep vein thrombosis

(< 0.1% [6 participants] in the AZD1222 group and < 0.1% [3 participants] in the placebo group).

No reports of Cerebral venous/Cerebral venous sinus thrombosis or Splanchnic vein thrombosis were identified in either the AZD1222 or placebo groups. When further analyzed by arterial, venous, and unspecified/mixed types of events, the numbers of participants were similar between the treatment groups in each type of event (arterial: 0.1% [13 participants]) in the AZD1222 group, < 0.1% [5 participants] in the placebo group; venous: < 0.1% [8 participants] in the AZD1222 group, < 0.1% [3 participants] in the placebo group; unspecified/mixed: < 0.1% [2 participants] in the AZD1222 group, < 0.1% [2 participants] in the placebo group) (see IEMT Table 372.1). The time to onset in the AZD1222 group ranged from 2 to 99 days following the first dose (median 18.5 days) and 13 to 64 days following the second dose (median 32 days). The time to onset in the placebo group ranged from 5 to 97 days following the first dose (median 26 days) and 32 to 71 days following the second dose (median 33.5 days). No concurrent AE of thrombocytopenia or platelet count decrease for participants were reported in participants with a thromboembolic AESI "Vascular".

12.2.5.4 Hematologic Events

In the pre-defined list of the AESI "Hematologic," thrombocytopenia was reported in 2 participants (<0.1%) in the AZD1222 group, and immune thrombocytopenia was reported in 1 participant (<0.1%) in the placebo group (see Table 14.3.2.6.1). None of these participants reported a concurrent thromboembolic event.

12.2.6 Additional Safety Analyses

Narrow and broad scope SMQ analyses were performed for the following: Demyelination, Peripheral neuropathy, Guillain-Barre Syndrome, Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous, Immune mediated/autoimmune disorders, Anaphylactic reaction, and Hypersensitivity, see Tables 14.3.2.29.1 and 14.3.2.18.1. For a summary of SMQ analyses (narrow and broad scope) by PT and blinding period, see Tables 14.3.2.18.2.7 and 14.3.2.29.2.7. For a summary of Nervous System Disorders by PT and blinding period, see Table 14.3.2.11.2.7. For a summary of Vascular Disorders of Embolism and Thrombosis by PT and blinding period, see Table 14.3.2.13.2.7.

For all SMQ analyses (narrow and broad scope), there were no clinically meaningful imbalances between the AZD1222 and placebo groups in the incidence of AESIs by category or PT for any category or PT not commonly associated with vaccination (see Tables 14.3.2.18.1, 14.3.2.29.1, 14.3.2.11.1, and 14.3.2.13.1).

In the Demyelination SMQ analysis, (narrow scope), 1 participant in the AZD1222 group reported 2 events (Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy) and 1 participant in the placebo group reported 1 event of Optic

neuritis (see Section 12.2.5.2 for additional information on these participants). When the SMQ analysis (broad scope) was applied, an additional 2 participants in the AZD1222 group were identified, each reporting a nonserious event of Trigeminal neuralgia.

In the Immune-mediated/autoimmune disorders SMQ analysis, (narrow scope), the incidence of participants with events was low in the AZD1222 and placebo groups (<0.1% [14 participants and <0.1% [3 participants], respectively). When analyzed by the SMQ (broad scope), the incidence was balanced between the AZD1222 (0.3% [67 participants]) and placebo (0.4% [41 participants]) groups.

In the Anaphylactic reaction SMQ analysis (narrow scope), no participants in either of the groups were identified. When the SMQ analysis (broad scope) was applied, the incidence of participants with events was low in the AZD1222 (3.0% [657 participants]) and placebo (3.2% [350 participants]) groups.

In the Hypersensitivity SMQ analysis, (narrow scope), a slightly higher incidence of events in the AZD1222 group compared with the placebo group was reported (2.4% [521 participants] vs 1.4% [156 participants], respectively). This difference was mainly driven by the PT of injection related reaction (1.5% [322 participants] vs 0.6% [64 participants], respectively). These events are consistent with the solicited AE profile that was observed, as described in Section 12.2.1.1. When analyzed by the SMQ (broad scope), the low incidence and numerical difference remained between in the AZD1222 and placebo groups (0.6% [137 participants]) vs placebo (0.8% [88 participants]).

In the Peripheral neuropathy SMQ analysis, (narrow scope), few participants were identified in AZD1222 and placebo groups (< 0.1% [9 participants] and < 0.1% [9 participants], respectively). When analyzed by the SMQ (broad scope), the proportion of participants with events within the Peripheral neuropathy SMQ analysis (broad scope) was low and similar in both the AZD1222 and placebo groups (0.5% [104 participants] and 0.4% [41 participants], respectively]). The most commonly reported events within this SMQ were hypoaesthesia (0.1% for both groups [31 participants and 10 participants, respectively]) and muscular weakness (< 0.1% for both groups [10 participants and 3 participants, respectively]).

In the Guillain-Barre syndrome SMQ analysis (narrow scope), one participant with 2 events (Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy) was identified in the AZD122 group; no participants in the placebo group were identified. When analyzed by the SMQ (broad scope), the proportion of participants with events was low and similar in the AZD1222 (0.7% [146 participants]) and placebo (0.5% [56 participants]) groups. Numerical differences were noted in the AZD1222 group compared with the placebo group in the SMQ analysis (broad scope) for the following events: hypoaesthesia (0.1% for both groups [31 participants vs 10 participants, respectively]), asthenia (<0.1% for both groups [22 participants and 5 participants, respectively]), and facial paralysis

(<0.1% [5 participants] vs 0 participants, respectively. Neurological AESIs, including facial paralysis, are discussed in Section 12.2.5.1.

The proportion of participants with events in the Embolic and thrombotic SMQ analysis (narrow scope) was low and similar in both in the AZD1222 and placebo groups (0.1% [23 participants] and < 0.1% [9 participants], respectively). Additional information regarding vascular events including when analyzed by the sub-SMQs of arterial, venous, and unspecified/mixed types of events is provided in Section 12.2.5.3.

For summaries of AEs for the SOCs of Nervous System Disorders, see IEMT Table 307.1. The proportions of participants with events in the SOCs of Nervous System Disorders were 8.2% (1773 participants) in the AZD1222 group and 6.5% (699 participants) in the placebo group. The apparent numerical imbalance in this SOC was driven by the PT of headache, which occurred at a higher incidence in the AZD1222 group compared with the placebo group (6.1% [1320 participants] vs 4.5% [491 participants], respectively). Of note, headache was one of the most frequently reported solicited systemic AEs (see Section 12.2.2.1). There was a numerical difference in the reporting of the following PTs, each of which were not reported in the placebo group: facial paralysis (< 0.1% [5 participants]), restless leg syndrome (< 0.1% [5 participants]), burning sensation (< 0.1% [4 participants]), depressed level of consciousness (< 0.1% [3 participants]), and hyperaesthesia (< 0.1% [3 participants]).

For summaries of AEs under HLGT Embolism and Thrombosis (including thrombotic, thromboembolic, and neurovascular events), see IEMT Table 307.5. Few events in the Vascular Disorders of Embolism and Thrombosis HLGT were reported in the AZD1222 and placebo groups (< 0.1% in each group [9 participants and 3 participants, respectively]). Of note, the PTs within the HLGT analysis were also included in the SMQ Embolic and thrombotic events. No clinically meaningful imbalances in the incidences of Embolism and Thrombosis HLGT by PT were observed.

Similar patterns to the overall SMQ analyses, SOC Nervous System Disorders, and HLGT Embolism and Thrombosis were observed when analyzed by subgroups of age, gender, race, and serostatus at baseline, where applicable.

12.3 Deaths, Serious Adverse Events, Discontinuation of Investigational Product Due to Adverse Events, and Other Significant Adverse Events

Summary tables and figures pertaining to this section are presented in Section 14.3.3 to Section 14.3.6 (Tables and Appendix 16.2).

All CSR participant narratives are presented in Appendix 16.2.7.1.

12.3.1 Deaths

For narratives for all deaths, see Appendix 16.2.7.1. For a summary of AEs and with an outcome of death by SOC, PT, and blinding period, see Table 40. For a summary of related AEs with an outcome of death by SOC, PT, and blinding period, see Table 14.3.2.1.4.7.

Overall, 14 participants reported SAEs with a fatal outcome during the blinded study period, including 7 participants in the AZD1222 group (7 events reported) and 7 participants in the placebo group (9 events reported; see Table 14.3.1.1.2.1). In addition, a fatal AE of chronic obstructive pulmonary disease was reported in 1 participant in the AZD1222 group post unblinding/ authorized COVID-19 vaccine administration; since this event took place post-unblinding, it was not included in the overall summary (see Table 14.3.2.1.5). In the AZD1222 group, AEs with a fatal outcome included overdose (2 participants; verbatim terms: PPD drug overdose and suspected drug overdose), toxicity to various agents (verbatim term: combined drug toxicity PPD), road traffic accident, toxic shock syndrome staphylococcal, accident (occurring in 1 participant each); in addition, 1 death was reported with PT of death (cause/aetiology unknown), occurring > 28 days following administration (second dose).

In the placebo group, AEs with a fatal outcome included COVID-19 pneumonia (2 participants), cardiac arrest, diabetic ketoacidosis, hemorrhagic transformation stroke, and asphyxia (occurring in 1 participant each); in addition, 1 death was reported with PT of death (cause of death was undetermined), occurring > 28 days following administration (second dose) (see Table 14.3.2.1.5).

None of the fatal events in either the AZD1222 or placebo groups were considered related to study intervention by the investigator (see Table 14.3.2.1.4.7 and Table 14.3.2.2.9).

For a list of all participants who had AEs with an outcome of death as of the data cut-off date, see Table 14.3.2.1.5.

Table 40 Adverse Events with an Outcome of Death by SOC, PT, and Blinding Period (Safety Analysis Set)

MedDRA version 23.1 System Organ Class Preferred Term	Number (%) of participants [E]					
	Double-blind Period		Unblinded Period		Overall	
	AZD1222 (N = 21587)	Placebo (N = 10792)	AZD1222 (N = 8832)	Placebo (N = 4860)	AZD1222 (N = 21587)	Placebo (N = 10792)
At least one AE with outcome of death	7 (< 0.1) [7]	7 (< 0.1) [9]	1 (< 0.1) [1]	0 [0]	8 (< 0.1) [8]	7 (< 0.1) [9]
Cardiac disorders	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Cardiac arrest	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
General disorders and administration site conditions	1 (< 0.1) [1]	1 (< 0.1) [1]	0 [0]	0 [0]	1 (< 0.1) [1]	1 (< 0.1) [1]
Death	1 (< 0.1) [1]	1 (< 0.1) [1]	0 [0]	0 [0]	1 (< 0.1) [1]	1 (< 0.1) [1]
Infections and infestations	1 (< 0.1) [1]	2 (< 0.1) [3]	0 [0]	0 [0]	1 (< 0.1) [1]	2 (< 0.1) [3]
COVID-19 pneumonia	0 [0]	2 (< 0.1) [2]	0 [0]	0 [0]	0 [0]	2 (< 0.1) [2]
Toxic shock syndrome staphylococcal	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]	0 [0]
Septic shock	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Injury, poisoning and procedural complications	5 (< 0.1) [5]	0 [0]	0 [0]	0 [0]	5 (< 0.1) [5]	0 [0]
Overdose	2 (< 0.1) [2]	0 [0]	0 [0]	0 [0]	2 (< 0.1) [2]	0 [0]
Accident	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]	0 [0]
Road traffic accident	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]	0 [0]

MedDRA version 23.1 System Organ Class Preferred Term	Number (%) of participants [E]					
	Double-blind Period		Unblinded Period		Overall	
	AZD1222 (N = 21587)	Placebo (N = 10792)	AZD1222 (N = 8832)	Placebo (N = 4860)	AZD1222 (N = 21587)	Placebo (N = 10792)
Toxicity to various agents	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]	0 [0]
Metabolism and nutrition disorders	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Diabetic ketoacidosis	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Nervous system disorders	0 [0]	1 (< 0.1) [2]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [2]
Haemorrhagic transformation stroke	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Ischaemic stroke	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Respiratory, thoracic and mediastinal disorders	0 [0]	1 (< 0.1) [1]	1 (< 0.1) [1]	0 [0]	1 (< 0.1) [1]	1 (< 0.1) [1]
Asphyxia	0 [0]	1 (< 0.1) [1]	0 [0]	0 [0]	0 [0]	1 (< 0.1) [1]
Chronic obstructive pulmonary disease	0 [0]	0 [0]	1 (< 0.1) [1]	0 [0]	1 (< 0.1) [1]	0 [0]

Note: The exposure period was calculated as (1) Double-blind period: time of first intervention to end of blinding period, (2) Unblinded period: date of unblinding/authorized COVID-19 vaccine administration to end of study, (3) Overall period: time of first intervention to end of study.

Note: Adverse events with an outcome of death were recorded from the time of signature of the informed consent form through the last participant contact.

Note: Adverse events were sorted alphabetically by SOC, and within each SOC, PTs are sorted by decreasing order of total frequency.

Note: Participants with more than one event within a SOC or PT were counted only once for that SOC or PT.

Note: Percentages were based on the number of participants in the analysis set by study arm and blinding period.

AE = adverse event; COVID-19 = coronavirus disease-2019; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class.

Source: Table 14.3.2.1.2.7

12.3.2 Medically Attended Adverse Events

For a summary of MAAEs and related MAAEs by SOC, PT, and blinding period, see Tables 14.3.2.7.2.7 and 14.3.2.8.1, respectively.

In the SAF, 7.5% of participants (1617 participants) in the AZD1222 group and 7.6% of participants (815 participants) in the placebo group reported an MAAE (see Table 14.3.2.7.1).

There were no clinical meaningful imbalances in the incidence of MAAEs by SOC or PT between the AZD1222 and placebo groups. The most frequently reported MAAEs by SOC in the AZD1222 group were in the SOCs of Infections and infestations (2.6% [558 participants] in the AZD1222 group and 2.9% [311 participants] in the placebo group) and Injury, poisoning and procedural complications (0.8% [172 participants]) in the AZD1222 group and 0.9% [95 participants] in the placebo group).

12.3.3 Serious Adverse Events

For all participants who had a SAE, including those with outcome of death, see Table 14.3.2.2.1.

In the SAF, < 1% of participants reported an SAE (0.6% of participants [140 participants] in the AZD1222 group and 0.7% of participants [78 participants] in the placebo group) (see Table 14.3.2.2.1). Only 1 participant in the AZD1222 group and 2 participants in the placebo group reported events that were considered related to study intervention, as determined by the investigator (see Section 12.3.3.1).

There were no clinically meaningful imbalances in the incidence of SAEs by SOC or PT between the AZD1222 and placebo groups (see Table 41).

Table 41 Serious Adverse Events (≥ 2 Participants in Either Treatment Group) by SOC and PT (Safety Analysis Set)

MedDRA version 23.1 System Organ Class Preferred Term	No. (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Total SAEs	140 (0.6) / 0.03	78 (0.7) / 0.03
Blood and lymphatic system disorders	3 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Anaemia	3 (< 0.1) / < 0.01	0
Blood loss anaemia	0	1 (< 0.1) / < 0.01

MedDRA version 23.1 System Organ Class Preferred Term	No. (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Cardiac disorders	15 (< 0.1) / < 0.01	12 (0.1) / < 0.01
Atrial fibrillation	3 (< 0.1) / < 0.01	4 (< 0.1) / < 0.01
Acute myocardial infarction	3 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Myocardial infarction	2 (< 0.1) / < 0.01	2 (< 0.1) / < 0.01
Coronary artery disease	3 (< 0.1) / < 0.01	0
Cardiac arrest	0	2 (< 0.1) / < 0.01
Supraventricular tachycardia	2 (< 0.1) / < 0.01	0
Gastrointestinal disorders	16 (< 0.1) / < 0.01	3 (< 0.1) / < 0.01
Intestinal obstruction	3 (< 0.1) / < 0.01	0
Gastrointestinal haemorrhage	2 (< 0.1) / < 0.01	0
Hepatobiliary disorders	3 (< 0.1) / < 0.01	2 (< 0.1) / < 0.01
Cholecystitis acute	2 (< 0.1) / < 0.01	0
Infections and infestations	37 (0.2) / < 0.01	28 (0.3) / < 0.01
COVID-19 pneumonia	3 (< 0.1) / < 0.01	10 (< 0.1) / < 0.01
Appendicitis	7 (< 0.1) / < 0.01	3 (< 0.1) / < 0.01
Pneumonia	7 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
COVID-19	1 (< 0.1) / < 0.01	5 (< 0.1) / < 0.01
Device related infection	2 (< 0.1) / < 0.01	2 (< 0.1) / < 0.01
Septic shock	3 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Urinary tract infection	3 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Cellulitis	2 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Pneumonia bacterial	2 (<0 .1) / < 0.01	0
Sepsis	2 (< 0.1) / < 0.01	0

MedDRA version 23.1 System Organ Class Preferred Term	No. (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Injury, poisoning and procedural complications	18 (< 0.1) / < 0.01	3 (< 0.1) / < 0.01
Joint dislocation	2 (< 0.1) / < 0.01	0
Overdose	2 (< 0.1) / < 0.01	0
Metabolism and nutrition disorders	1 (< 0.1) / < 0.01	8 (< 0.1) / < 0.01
Diabetic ketoacidosis	1 (< 0.1) / < 0.01	2 (< 0.1) / < 0.01
Hyponatraemia	0	2 (< 0.1) / < 0.01
Musculoskeletal and connective tissue disorders	5 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (< 0.1) / < 0.01	8 (< 0.1) / < 0.01
Prostate cancer	3 (< 0.1) / < 0.01	2 (< 0.1) / < 0.01
Invasive ductal breast carcinoma	2 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Papillary thyroid cancer	3 (< 0.1) / < 0.01	0
Lung neoplasm malignant	2 (< 0.1) / < 0.01	0
Nervous system disorders	11 (< 0.1) / < 0.01	5 (< 0.1) / < 0.01
Ischaemic stroke	4 (< 0.1) / < 0.01	1 (< 0.1) / < 0.01
Pregnancy, puerperium and perinatal conditions	2 (< 0.1) / < 0.01	0
Abortion spontaneous	2 (< 0.1) / < 0.01	0
Psychiatric disorders	3 (< 0.1) / < 0.01	6 (< 0.1) / < 0.01
Anxiety	0	2 (< 0.1) / < 0.01
Suicidal ideation	2 (< 0.1) / < 0.01	0
Suicide attempt	0	2 (< 0.1) / < 0.01
Renal and urinary disorders	3 (< 0.1) / < 0.01	4 (< 0.1) / < 0.01
Acute kidney injury	1 (< 0.1) / < 0.01	3 (< 0.1) / < 0.01
Reproductive system and breast disorders	0	2 (< 0.1) / < 0.01

MedDRA version 23.1 System Organ Class Preferred Term	No. (%) of participants / Adj rate	
	AZD1222 (N = 21587)	Placebo (N = 10792)
Respiratory, thoracic and mediastinal disorders	9 (< 0.1) / < 0.01	3 (< 0.1) / < 0.01
Chronic obstructive pulmonary disease	2 (< 0.1) / < 0.01	0
Pulmonary embolism	2 (< 0.1) / < 0.01	0
Vascular disorders	3 (< 0.1) / <0.01	3 (< 0.1) / < 0.01
Deep vein thrombosis	2 (< 0.1) / < 0.01	0

Note: Exposure-adjusted rate (Adj. Rate) was calculated as number of participants with AEs/total patient-years of observation. Patient-years were determined by summing the total number of follow-up days of each participant in the treatment group, and then dividing by 365.25. The exposure period was calculated from time of first intervention to end of study.

Note: SAEs were recorded from the time of signature of the informed consent form through the last participant contact. SAEs reported after participant unblinding/authorized COVID-19 vaccine administration were excluded.

Note: AEs were sorted alphabetically by SOC, and within each SOC, PTs were sorted by decreasing order of total frequency.

Note: Participants with more than one event within a SOC or PT were counted only once for that SOC or PT.

Note: Percentages were based on the number of participants in the analysis set by study arm.

Adj. = adjusted; AE = adverse event; COVID-19 = coronavirus disease-2019; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SOC = system organ class.

Source: Table 14.3.2.2.1

12.3.3.1 Serious Adverse Events Related to Study Intervention

For narratives of related SAEs, see Appendix 16.2.7.1. For a summary of SAEs and related SAEs by SOC, PT, and blinding period, see Tables 14.3.2.2.2.7 and 14.3.2.2.6.7, respectively.

Few participants (1 in the AZD1222 group [2 events] and 2 in the placebo group [2 events]) reported SAEs that were considered related to study intervention, as determined by the investigator (see Table 14.3.1.1.2.1). In the AZD1222 group, 1 participant reported related events of hypoaesthesia and chronic inflammatory demyelinating polyradiculoneuropathy (see Table 14.3.2.2.9). For additional information on the participant reporting related SAEs of hypoaesthesia and chronic inflammatory demyelinating polyradiculoneuropathy, see Section 12.2.5.2 (PIMC – Neuroinflammatory Disorders). One other participant in the AZD1222 group reported a related SAE of paraesthesia; however, because this event took place post-unblinding, it was not included in the overall summary (see Table 14.3.2.2.9 for additional detail on the SAE of paraesthesia for participant PPD . In the placebo group, 1 participant each reported a related SAE of optic ischaemic neuropathy and neurosensory hypoacusis.

For a listing of SAEs see Table 14.3.2.2.9.

12.3.4 Discontinuations of Investigational Product Due to Adverse Events

In the SAF, a total of 1.2% (266 participants) in the AZD1222 group and 1.5% (162 participants) in the placebo group discontinued study intervention due to AEs following any dose, with the majority reported in the SOCs of infections and infestations (1.0% [225 participants] in the AZD1222 group and 1.3% [145 participants] in the placebo group) (see Table 14.3.2.3.1). The most common AEs leading to discontinuation of study intervention by PT were COVID-19 (0.9% [198 participants] in the AZD1222 group and 1.2% [131 participants] in the placebo group) and asymptomatic COVID-19 (< 0.1% [21 participants] in the AZD1222 group and < 0.1% [9 participants] in the placebo group).

In the SAF, the incidence of study discontinuation was low; a total of < 0.1% (3 participants; 1 each with PTs of accident, overdose, and road traffic accident) in the AZD1222 group and < 0.1% (5 participants; 2 with PT of COVID-19 pneumonia and 1 each with PTs of diabetic ketoacidosis, hemorrhagic transformation stroke, and asphyxia) in the placebo group discontinued the study due to AEs within 28 days following any dose (see Table 14.3.1.1.1.1 and Table 14.3.2.4.1). For a summary of SAEs, MAAEs, and AESIs and related SAEs, MAAEs, and AESIs leading to study discontinuation by SOC, PT, and blinding period, see Table 14.3.2.4.7 and Table 14.3.2.4.8.8.

12.4 Clinical Laboratory Evaluation

Clinical laboratory tests were not evaluated in this study.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

Summary tables and figures pertaining to this section are presented in Section 14.3.8 (see Tables 14.3.4.1 and 14.3.4.2) and Appendix 16.2.

Data collected through the digital health device on heart rate, respiratory rate, temperature, and oxygen saturation level were recorded as exploratory efficacy measurements (see Section 14.1.2.3) and were only reported as AEs if changes resulted in MAAEs or SAEs. Overall, vital signs remained within normal ranges and no clinically meaningful changes from baseline were identified during the study (see Tables 14.3.4.1 and 14.3.4.2).

12.5.1 Physical Findings and Other Observations Related to Safety

Physical examinations (completed and targeted) were conducted as per the schedules of activities (refer to Table 5, Table 6, Table 7, and Table 8). Clinically significant

findings/changes will be summarized though the medical history summary or AE summaries, as appropriate. No summaries were specifically provided for general physical examinations.

A listing of chest imaging results for participants with a chest imaging assessment was provided, with assessments occurring after unblinding/authorized COVID-19 vaccine administration flagged (see Listing 16.2.8).

12.6 Pregnancies

As of 05 March 2021, a total of 17 pregnancies were reported in the AZD1222 analysis dataset, with 15 participants in the AZD1222 group and 2 participants in the placebo group (see Listing 16.2.4.3). In the AZD1222 group, 1 termination of pregnancy and 2 spontaneous miscarriages were reported. In the placebo group, there were 0 reports of termination of pregnancy or of spontaneous miscarriage. A review of the pregnancy exposure reports did not raise any safety concerns.

12.7 Safety Evaluation Conclusions

- Overall, vaccination with AZD1222 was well tolerated.

12.7.1 Exposure

- The proportion of participants at risk was balanced for all durations of follow up, with > 90% of participants having had at least 60 days of follow up post first dose.
- Overall, participants in the AZD1222 group had a median duration of follow up post second dose of 61.0 days, and participants had a median duration of follow up post first dose of 92.0 days, regardless of unblinding events. The duration of follow up was balanced between treatment groups.

12.7.2 Safety and Tolerability

Solicited and unsolicited AEs

- The majority of solicited (local and systemic) AEs and unsolicited AEs following vaccination with AZD1222 were mild or moderate in severity.
- Reactogenicity, as evaluated by the incidence of solicited AEs for 7 days post each dose, was lower following the second dose in both treatment groups.
  - Solicited local and systemic AEs were reported by 74.1% (1440 participants) and 71.6% of participants (1395 participants), respectively, within the first 7 days following any vaccination with AZD1222.
  - In the placebo group, solicited local injection site and systemic AEs were reported by 24.4% (239 participants) and 53.0% of participants (519 participants), respectively.
  - Most of the solicited local and systemic AEs following vaccination with AZD1222 were of short duration and mild or moderate in severity.

- The reactogenicity safety profile of AZD1222 was generally similar in older adults ≥ 65 years compared with younger adults aged 18 to 64 years of age; however, older adults reported milder and less frequent solicited reactogenic AEs compared with younger adults. There were no clinically meaningful differences observed in any other subgroup categories.
- Unsolicited AEs were consistent with AEs commonly observed following vaccination:
  - Unsolicited AEs were reported in 40.6% of participants (8771 participants) in the AZD1222 group and 29.7% of participants (3201 participants) in the placebo group within 28 days following any dose. In the AZD1222 group, there were 26.6% of participants (5736 participants) with an unsolicited AE within 28 days of the first dose and 24.4% of participants (5074 participants) within 28 days of the second dose.
  - The most frequently reported unsolicited AEs in the AZD1222 group were pain, headache, injection site pain, fatigue, and body temperature increased; all of which were reported at a higher frequency in the AZD1222 group compared with the placebo group.
  - The majority of unsolicited events were mild to moderate in severity. The proportion of events with severe or life-threatening severity was 1.0% (225 participants) in the AZD1222 group and 1.1% (116 participants) in the placebo group after any dose.
  - Related AEs, as determined by the investigator, were reported in 28.9% of participants (6238 participants) in the AZD1222 group and 14.1% of participants (1525 participants) in the placebo group following any dose. Related AEs were most commonly mild to moderate in severity.

<u>Deaths, SAEs, MAAEs, and AEs leading to discontinuation</u>

- Overall, 14 participants reported SAEs with a fatal outcome during the blinded study period, including 7 participants in the AZD1222 group (7 events reported) and 7 participants in the placebo group. None of the fatal events in either the AZD1222 or placebo groups were considered related to study intervention by the investigator.
- Overall, < 1% of participants reported an SAE (0.6% of participants [140 participants] in the AZD1222 group and 0.7% of participants [78 participants] in the placebo group). Only 1 participant in the AZD1222 group and 2 participants in the placebo group reported SAEs that were considered related to study intervention, as determined by the investigator. There were no clinically meaningful imbalances in the incidence of SAEs by SOC or PT between the AZD1222 and placebo groups.
- Overall, 7.5% of participants (1617 participants) in the AZD1222 group and 7.6% of participants (815 participants) in the placebo group reported an MAAE. There were no clinical meaningful imbalances in the incidence of MAAEs by SOC or PT between the AZD1222 and placebo groups.
- The incidence of study discontinuation due to an AE was low; a total of < 0.1% (3 participants) in the AZD1222 group and < 0.1% (5 participants) in the placebo group discontinued the study due to AEs within 28 days following any dose.

Adverse events of special interest

- The incidence of AESI was low (2.4% of participants [525 participants] in the AZD1222 group and 3.9% of participants [416 participants] in the placebo group). There were no clinically meaningful imbalances in the incidence of AESIs by category or PT.
  - There were 3 fatal events categorized as AESIs reported in the placebo group (2 participants reported the PT of COVID-19 pneumonia and 1 participant reported the PT of haemorrhagic transformation stroke) and 0 fatal events reported in the AZD1222 group.
  - In the pre-defined list of the AESI "Neurologic" category, the proportion of participants who reported neurological AESIs was similar between the AZD1222 (0.5% [114 participants]) and placebo (0.4% [48 participants]) groups.
  - In the pre-defined list of the AESI "PIMC" category, the proportion of participants who reported PIMC AESIs was lower in the AZD1222 group (1.8% [393 participants]) compared with the placebo group (3.4% [366 participants]).
    - Neuroinflammatory disorders were reported by < 0.1% of participants in both the AZD1222 and placebo groups (8 and 1 participants, respectively).
    - The most frequently reported PT, facial paralysis, was reported by 5 and 0 participants in the AZD1222 and placebo groups, respectively. Of the 5 participants in the AZD1222 group, 2 participants reported PTs of facial paralysis after receiving only the first dose of study intervention, while 3 participants reported Bell's palsy post second dose. One participant reported potential immune-mediated neurological (demyelinating) conditions; the PTs reported by this participant in the AZD1222 group were chronic inflammatory demyelinating polyradiculoneuropathy and Guillain Barre syndrome.
    - One AESI of VIth nerve paralysis was reported in the AZD1222 group, which was nonserious and considered by the investigator to be not related to AZD1222.
    - During the double-blind period, events in the PIMC/VAERD category were reported by a numerically higher percentage of participants in the placebo group (3.4% [362 participants) compared with the AZD1222 group (1.7% [374 participants]). The most frequently reported PT was COVID-19 in both the AZD1222 (1.7% [368 participants] and placebo groups (3.3% [354 participants]), followed by COVID-19 pneumonia which was reported by < 0.1% (6 participants) in the AZD1222 group and 0.2% (17 participants) in the placebo group.
  - In the pre-defined list of the AESI "Vascular" category, few events were reported (0.1% [23 participants] in the AZD1222 group and < 0.1% [9 participants] in the placebo group); no imbalance was observed in this AESI category.
    - During the double-blind period, the most frequently reported PT (≥ 5 participants in the AZD1222 group) within the category of vascular events was deep vein thrombosis (< 0.1% [6 participants] in the AZD1222 group and < 0.1% [3 participants] in the placebo group). No reports of Cerebral

venous/Cerebral venous sinus thrombosis or Splanchnic vein thrombosis were identified in either the AZD1222 or placebo groups. No concurrent AE of thrombocytopenia or platelet count decrease for participants were reported in participants with a thromboembolic AESI "Vascular" category.

- In the pre-defined list of the AESI "Hematologic" category, thrombocytopenia was reported in < 0.1% (2 participants) in the AZD1222 group, and immune thrombocytopenia was reported in < 0.1% (1 participant) in the placebo group. None of these participants reported a concurrent thromboembolic event.

Pregnancies

- As of the data cut-off date, pregnancies were reported in 15 participants in the AZD1222 group and 2 participants in the placebo group. In the AZD1222 group, 1 termination of pregnancy and 2 spontaneous miscarriages were reported. In the placebo group, there were 0 reports of termination of pregnancy or of spontaneous miscarriage. A review of the pregnancy exposure reports did not raise any safety concerns.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

Effective vaccines against COVID-19 are the optimal strategy to guarantee a safe and sustained exit strategy from repeated lockdowns. AZD1222 is being developed by AstraZeneca for the prevention of COVID-19. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tPA leader sequence at the N terminus. Study D8110C00001 is an ongoing double-blind, placebo-controlled, randomized study in adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and are at increased risk for SARS CoV-2 acquisition and COVID-19. Participants received 2 doses of AZD1222 or saline placebo 4 weeks apart. This interim CSR provides available safety, efficacy, and immunogenicity data from the full primary analysis (clinical database cut-off date of 05 Mar 2021) and the 2-month median follow up post the second dose of study intervention. A pre-planned interim analysis was included to support early assessment of efficacy prior to reaching the 150 events required for the primary analysis.

Study D8110C00001 is a randomized, double blind, placebo-controlled, multicenter phase of the study assessing the efficacy, safety, and immunogenicity of AZD1222 compared with saline placebo for the prevention of COVID-19. As of the cut-off date of 05 March 2021, 32379 participants had been randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp AZD1222 or saline placebo 4 weeks apart, on Days 1 and 29. Randomization was stratified by age (≥ 18 and < 65 years, and ≥ 65 years), with planned enrollment of at least 25% of

participants in the older age stratum. Overall, 21583 and 10796 participants received AZD1222 or placebo, respectively, and nearly all (96.7%) participants were ongoing in the study at the time of data cut-off date. Note: Study D8110C00001 was placed on clinical hold on 09 September 2020 due to an event of transverse myelitis reported in the University of Oxford-sponsored study COV002. The FDA deemed it was safe to remove the clinical hold on 23 October 2020. The consequence of this hold is that approximately 800 study participants had a dosing interval > 4 weeks.

The first participants randomized in each age group in the USA, including 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy assessing the reactogenicity and immunogenicity of AZD1222.

The demographic characteristics in the FVS were generally similar among participants who received AZD1222 and placebo, and the study population was representative of the intended target population. At screening, participants were evaluated for the presence of pre-defined risk factors associated with comorbidities based on presence or absence of CDC risk factors for severe COVID-19 disease. These characteristics were generally similar among participants who received AZD1222 and placebo; the most common comorbidities were obesity, high blood pressure, a history of smoking, and asthma. The median dosing interval was 29.0 days for both study intervention groups using the overall SAF and when limited to those participants who were randomized after clinical hold. A total of 516 participants and 250 participants in the AZD1222 and placebo groups, respectively, were randomized prior to the clinical hold; the median dosing intervals were 60.0 days and 59.0 days, respectively.

13.1.1 Efficacy

Regardless of unblinding events, the median duration of follow up in the FAS from the second dose in the AZD1222 group was 61 days, and median duration of follow up from the first dose was 92 days. For the placebo group, the median duration of follow up from the second dose was identical (61 days) and similar (91 days) from the first dose. Similar median durations of follow up were observed when duration of follow up was evaluated by age group (18 to < 65 years and ≥ 65 years).

The robust vaccine efficacy of AZD1222 was consistently demonstrated through the following results:

Primary endpoint

In the primary efficacy analysis using the 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 RT-PCR-positive symptomatic illness, with a 2-sided nominal p-value of < 0.001 for testing H0: VE = 30%, which met the pre-specified success criterion (Falsey 2021a).

The results from the multiple imputation sensitivity analysis (when the observed event rate from the randomized study arm was applied) demonstrated a VE estimate that was consistent with the primary efficacy analysis (73.3%).

The results from the 4 supplementary analyses demonstrated VE estimates that were consistent with the primary efficacy analysis (point estimates approximately 74.0%) and included time to first event and changes to which participants were included in the analysis (ie, analysis set, participants whose second dose timing was impacted by clinical hold, and contribution of different data that were considered during adjudication). Of note, the results from the primary efficacy analysis excluding participants whose second dose was out of window due to the clinical hold suggests that the delay in the second dose did not have a clinically meaningful difference on VE for those participants who received the second dose outside of the planned 4-week interval.

Analyses across relevant subgroups showed a consistent conclusion of VE relative to the overall population, including subgroups based on age, gender, ethnicity, BMI, and presence of pre-defined comorbidities.

Secondary endpoints

All key secondary endpoints were statistically significant such that each of the 2-sided 95% CIs for the VE estimates were > 0%, using the hierarchical fixed-sequence testing method and were analyzed for events ≥ 15 days post second dose of study intervention. For the first case of SARS-CoV-2 RT-PCR positive symptomatic illness regardless of evidence of prior SARS-CoV-2 infection, there were 76 COVID-19 cases in the AZD1222 group and 135 COVID-19 cases in the placebo group, with a VE of 73.7%. There were no cases of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness in the AZD1222 group (VE estimate of 100.0%; the incidence of COVID-19-related emergency department visits was low in the AZD1222 group [VE estimate of 94.8%]). The incidence of the first post-treatment response for SARS-CoV-2 Nucleocapsid antibodies regardless of symptoms, was 156 COVID-19 cases in the AZD1222 group and 202 COVID-19 cases in the placebo group, with a VE estimate of 64.3%.

Evaluation of efficacy using the CDC or University of Oxford-defined criteria resulted in consistent conclusions relative to the primary efficacy analysis (VE estimates of 69.7% and 70.7%, respectively). Efficacy following the first dose demonstrated a VE estimate of 54.5% against symptomatic illness and a VE estimate of 85.0% against severe or critical illness.

Exploratory endpoints

At ≥ 15 days post second dose in the FVS and post first dose in the FAS, respectively, high VE estimates were demonstrated for hospitalizations (94.2% and 80.0%, which includes ICU and non-ICU admissions) and ICU-admissions (100.0% and 75.7%). The VE estimate for COVID-19 death was 100.0%.

A total of 88 of the 203 cases in the FVS had interpretable lineage data available, and the resulting VE within this subgroup was consistent with the updated primary efficacy analysis (77.2%). A limited number of variants of concern were identified within the FAS who were seronegative at baseline as of the data cut-off date (05 March 2021). Two cases of B.1.1.7 (Alpha) were observed, and one case of B.1.351 (Beta) was identified. No cases of lineage B.1.1.28.1 (ie, P.1; Gamma) were identified through sequencing of saliva samples. Of the WHO-designated Variants of Interest, B.1.427, B.1.429, and B.1.526 (Iota) were observed in the FAS, with B.1.429 being the most frequent (with 14 cases observed). No cases of the B.1.617.1 lineage (Kappa) or the B.1.617.2 (Delta) lineage were detected. Vaccine efficacy will continue to be evaluated in variants of concern and variants of interest for the 6-month median follow up analysis and provided in a CSR addendum.

Time to clearance of SARS-CoV-2 in saliva samples in AZD1222 vaccinated participants (n = 52) was notably shorter (median 11 vs 16 days) compared with participants in the placebo group (n = 92) when the cumulative incidence of shedding was examined in study participants in the FVS with cases occurring ≥ 15 days post second dose. These data suggest that in addition to reducing the incidence of COVID-19 disease, even in those study participants who have breakthrough infections, SARS-CoV-2 is shed for a shorter amount of time in AZD1222 recipients, potentially reducing the length of time vaccinated individuals are capable of transmitting infection.

13.1.2 Immunogenicity

To assess the immunogenicity of AZD12222, the first participants randomized in each age group in the USA, including 1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, also participated in a Substudy.

AZD1222 generated a strong humoral response, including when stratified by age, race, and with longer dose intervals. Geometric mean titers of S-binding and RBD-binding antibodies peaked at 14 days post second dose (24224.11 AU/mL and 29487.39 AU/mL, respectively) of AZD1222 and were maintained above the levels achieved by the first dose through D90. Pseudoneutralizing antibody responses were elevated above baseline at 14 days post first dose of AZD1222 (GMT = 41.37 AU/mL) but had slightly different kinetics of induction as compared to S binding responses, with responses peaking at 28 days post second dose (GMT = 245.56 AU/mL) instead of at 14 days post second dose.

13.1.3 Safety

As of the data cut-off date of 05 March 2021, a total of 99.8% of participants (32379 participants) were included in the SAF based on actual study intervention received; 21587 participants received AZD1222 and 10792 participants received placebo. Overall, vaccination with AZD1222 was well tolerated.

In the AZD1222 group, participants had a median duration of follow-up post second dose of 61.0 days and a median duration of follow-up post first dose of 92.0 days, regardless of unblinding events. The duration of follow-up was similar for participants the placebo group.

A total of 1956 participants in the AZD1222 group and 981 participants in the placebo group were included in a Substudy, with additional assessments for pre-defined solicited AEs for 7 days post each dose of study intervention. Solicited local and systemic AEs were reported by 74.1% and 71.6% of Substudy participants, respectively, within the first 7 days following any vaccination with AZD1222. In the placebo group, solicited local injection site and systemic AEs were reported by 24.4% and 53.0% of participants, respectively. Most of the solicited local and systemic AEs following vaccination with AZD1222 were mild (Grade 1) or moderate (Grade 2) in severity. The most frequently reported solicited local injection site AEs within 7 days after any dose with AZD1222 were pain (58.3% vs 15.7% in placebo) and tenderness (68.4% vs 19.0% in placebo). The most frequently reported solicited systemic AEs within 7 days after either dose with AZD1222 were fatigue (49.7% vs 31.2% in placebo), and headache (50.2% vs 35.5% in placebo). In the AZD1222 group, solicited local and systemic AEs were reported less frequently within 7 days post second dose (53.4% of participants and 47.3% of participants, respectively) than post first dose (68.3% of participants and 64.7% of participants, respectively). In the AZD1222 and placebo groups, when compared with the first dose, solicited local and systemic AEs reported post second dose were milder and reported less frequently.

The reactogenicity safety profile of AZD1222 was generally similar in older adults ≥ 65 years compared with younger adults aged 18 to 64 years of age; however, older adults reported milder and less frequent solicited reactogenic AEs compared with younger adults. There were no clinically meaningful differences observed in any other subgroup categories.

In the SAF, 40.6% of participants in the AZD1222 group and 29.7% of participants in the placebo group reported an unsolicited AE within 28 days following any dose. In the AZD1222 group, there were 26.6% of participants with an unsolicited AE within 28 days of the first dose and 24.4% of participants within 28 days of the second dose. The majority of the unsolicited events were mild (Grade 1) or moderate (Grade 2) in severity; the proportion of events severe or life-threatening (≥ Grade 3) in severity was 1.0% in the AZD1222 group and 1.1% in the placebo group after any dose. Related AEs, as determined by the investigator, were reported in 28.9% of participants in the AZD1222 group and 14.1% of participants in the placebo group following any dose; related AEs were most commonly mild or moderate in severity.

The frequency of AEs leading to discontinuation from study intervention or study discontinuation was similar between the AZD1222 and placebo groups. Serious AEs were reported in 0.5% of participants each in the AZD1222 and placebo groups. One participant

each in both the AZD1222 and placebo groups reported a related SAE, as determined by the investigator. A total of 15 SAEs with a fatal outcome (8 out of 21587 participants in the AZD1222 group and 7 out of 10792 participants in the placebo group) occurred as of the cut-off date, irrespective of the blinding period. Adverse events of special interest occurred in 2.0% of participants in the AZD1222 group and 3.0% of participants in the placebo group. Medically attended AEs were reported by 6.0% of participants in the AZD1222 group and 5.9% of participants in the placebo group. Adverse events reported within 28 days following any dose (SAEs, MAAEs, and AESIs) were balanced between the AZD1222 and placebo groups.

In the pre-defined list of the AESI "Vascular," few events were reported. No reports of Cerebral venous/Cerebral venous sinus thrombosis or Splanchnic vein thrombosis were identified in the AZD1222 group. No concurrent AE of thrombocytopenia or platelet count decrease for participants who reported a thromboembolic event were reported.

As of the data cut-off date, a total of 17 pregnancies were reported in the AZD1222 analysis dataset, with 15 participants in the AZD1222 group and 2 participants in the placebo group. A review of the pregnancy exposure reports did not raise any safety concerns.

13.2 Overall Conclusions

- As of the data cut-off date of 05 March 2021, when administered as 2 IM doses of 5×10^{10} vp at an interval of approximately 4 weeks, the AZD1222 vaccine demonstrated a high degree of efficacy compared with saline placebo for the prevention of COVID-19 and SARS-CoV-2 infection.
  - In the primary efficacy analysis with 203 adjudicated cases, AZD1222 showed a VE estimate of 74.0% against SARS-CoV-2 RT-PCR-positive symptomatic illness.
  - Vaccine efficacy estimates across subgroups based on age, gender, ethnicity, BMI, and presence of pre-defined comorbidities were consistent with the VE estimate for the overall population.
- Overall, AZD1222 generated a strong humoral response, including when stratified by age, race, and ethnicity.
- The AZD1222 vaccine had an acceptable safety profile and was well tolerated in healthy adult participants, as well as in high-risk adult populations of older adults and adults with comorbidities, who have an increased risk of death and severe disease associated with COVID-19.
  - Unsolicited AEs were consistent with AEs commonly observed following vaccination. The majority of solicited (local and systemic) AEs and unsolicited AEs following vaccination with AZD1222 were mild or moderate in severity and completely resolved within 2 to 3 days. Reactogenicity, as evaluated by the incidence of solicited AEs for 7 days post each dose, was lower following the second dose.

– The incidences of SAEs and AESIs were low, and there were no clinically meaningful imbalances in the incidence of AESIs between the AZD1222 and placebo groups.

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14.3.5 Discontinuation of Investigational Product Due to Adverse Events

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14.3.6 Adverse Events of Special Interest

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14.3.8 Additional Safety Analyses

14.3.8.1 Summary Tables of Additional Safety Analyses

14.3.8.2 Listings of Additional Safety Analyses

14.3.9 Vital Signs, Physical Findings, and Other Observations

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16. APPENDICES

16.1 Study Information

16.2 Subject Data Listings and Narratives

16.3 Case Report Forms

16.4 Individual Subject Data Listings

16.5 Adjudication Data