ORIGINAL ARTICLE

Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine

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ABSTRACT

BACKGROUND

The safety and efficacy of the AZD1222 (ChAdOx1 nCoV-19) vaccine in a large, diverse population at increased risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the United States, Chile, and Peru has not been known.

METHODS

In this ongoing, double-blind, randomized, placebo-controlled, phase 3 clinical trial, we investigated the safety, vaccine efficacy, and immunogenicity of two doses of AZD1222 as compared with placebo in preventing the onset of symptomatic and severe coronavirus disease 2019 (Covid-19) 15 days or more after the second dose in adults, including older adults, in the United States, Chile, and Peru.

RESULTS

A total of 32,451 participants underwent randomization, in a 2:1 ratio, to receive AZD1222 (21,635 participants) or placebo (10,816 participants). AZD1222 was safe, with low incidences of serious and medically attended adverse events and adverse events of special interest; the incidences were similar to those observed in the placebo group. Solicited local and systemic reactions were generally mild or moderate in both groups. Overall estimated vaccine efficacy was 74.0% (95% confidence interval [CI], 65.3 to 80.5; P<0.001) and estimated vaccine efficacy was 83.5% (95% CI, 54.2 to 94.1) in participants 65 years of age or older. High vaccine efficacy was consistent across a range of demographic subgroups. In the fully vaccinated analysis subgroup, no severe or critical symptomatic Covid-19 cases were observed among the 17,662 participants in the AZD1222 group; 8 cases were noted among the 8550 participants in the placebo group (<0.1%). The estimated vaccine efficacy for preventing SARS-CoV-2 infection (nucleocapsid antibody seroconversion) was 64.3% (95% CI, 56.1 to 71.0; P<0.001). SARS-CoV-2 spike protein binding and neutralizing antibodies increased after the first dose and increased further when measured 28 days after the second dose.

CONCLUSIONS

AZD1222 was safe and efficacious in preventing symptomatic and severe Covid-19 across diverse populations that included older adults. (Funded by AstraZeneca and others; ClinicalTrials.gov number, NCT04516746.)

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*A complete list of the members of the AstraZeneca AZD1222 Clinical Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Previous clinical trials have shown the safety and efficacy of the AZD1222 (ChAdOx1 nCoV-19) vaccine in preventing coronavirus disease 2019 (Covid-19) in diverse epidemiologic settings, including Brazil and the United Kingdom.[1-3] Accordingly, AZD1222 is being distributed for vaccination in more than 100 countries across six continents and has been administered to hundreds of millions of persons.[4]

We report results from the primary analysis of a pivotal phase 3, double-blind, placebo-controlled trial that assessed the safety, efficacy, and immunogenicity of two doses of AZD1222 administered 4 weeks apart for the prevention of symptomatic Covid-19 confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing. This trial of AZD1222 was designed to include diverse groups at high risk for exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and populations at increased risk for Covid-19 complications.

Methods

Trial Oversight

This is an ongoing phase 3, double-blind, placebo-controlled trial conducted at 88 sites in the United States, Chile, and Peru in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The trial protocol (available with the full text of this article at NEJM.org) and six amendments were approved by the ethics committee or institutional review board at each center, and all participants provided written informed consent before enrollment. Safety is reviewed on a continual basis. Data were gathered by the trial site investigators in collaboration with a contract research organization (IQVIA) and AstraZeneca and analyzed by IQVIA and AstraZeneca. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All authors contributed to the writing and editing of the manuscript and reviewed and approved the manuscript for submission. Medical writing assistance was funded by AstraZeneca. Agreements requiring authors to maintain data confidentiality were in place between the sponsor and the authors.

Trial Design and Population

The trial was designed by AstraZeneca in collaboration with the Department of Health and Human Services and the National Institutes of Health and the trial cochairs.[5,6] The objectives of the trial were to assess the safety, efficacy, and immunogenicity of AZD1222 as compared with placebo for the prevention of symptomatic Covid-19 in participants 18 years of age or older whose conditions were medically stable and who were at increased risk for SARS-CoV-2 infection, including high risk for symptomatic and severe Covid-19. Key inclusion and exclusion criteria along with definitions and descriptions of testing protocols are provided in the Supplementary Appendix, available at NEJM.org.

Participants received two intramuscular injections of either AZD1222 (5×10^{10} viral particles) or saline placebo administered 4 weeks apart on days 1 and 29 (–3 to +7 days). Random assignment was in a 2:1 ratio to increase the number of participants who received AZD1222. Randomization was stratified according to age (≥18 to 64 years and ≥65 years), with a target of 25% or more of the participants 65 years of age or older. The safety analysis population was defined as all participants who received at least one dose of AZD1222 or placebo, with participants grouped according to the actual vaccine or placebo received. The fully vaccinated analysis population included all participants who were SARS-CoV-2 seronegative at baseline, who received two doses of vaccine or placebo, and who remained in the trial for 15 days or more after their second dose and did not have a previous confirmed SARS-CoV-2 RT-PCR–positive infection.

Participants were reminded weekly to monitor for Covid-19 symptoms. Participants who had one or more qualifying symptoms of Covid-19 underwent illness evaluations and SARS-CoV-2 testing. All trial participants were scheduled to have serum collected for SARS-CoV-2 antibody testing to assess the efficacy of the vaccine, regardless of the presence or severity of symptoms. All participants will remain in the study for 2 years (730 days) after receipt of the first dose of AZD1222 or placebo for safety follow-up and assessment of durability of immune response.

A substudy to further assess reactogenicity and immunogenicity of AZD1222 included the

first participants who underwent randomization in each age group in the United States (1500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants 70 years of age or older). These participants completed symptom diaries after vaccination and had additional blood samples obtained on days 15 and 43.

SAFETY AND REACTOGENICITY

Unsolicited adverse events were recorded for all participants for 28 days after each dose of AZD1222 or placebo, and serious adverse events will be recorded from the time of signed informed consent through day 730. Medically attended adverse events and adverse events of special interest will be recorded from day 1 after the first dose through day 730. Reactogenicity was evaluated in the substudy group to investigate the incidence of solicited local and systemic adverse events for 7 days after each dose of AZD1222 or placebo.

EFFICACY

The primary efficacy end point was the first occurrence of SARS-CoV-2 symptomatic illness, confirmed by positive results on RT-PCR testing, with onset 15 days or more after the second dose of vaccine or placebo among participants who were seronegative for Covid-19 at baseline (descriptions of end points and analyses are provided in the Supplementary Appendix). Estimated vaccine efficacy was analyzed according to demographic subgroups of interest.

Key secondary end points included the incidence of symptomatic illness (at 15 days or more after the second dose) regardless of evidence of previous SARS-CoV-2 infection at baseline, severe or critical symptomatic Covid-19, Covid-19–related emergency department visits, symptomatic Covid-19 as defined by Centers for Disease Control and Prevention (CDC) criteria, and SARS-CoV-2 infection regardless of symptoms or severity, measured as a post-treatment serologic response (negative at baseline and positive after baseline) for SARS-CoV-2 nucleocapsid antibodies. Estimated vaccine efficacy was analyzed for exploratory end points, including the incidence of Covid-19–related hospitalizations and intensive care unit (ICU) admissions.

HUMORAL IMMUNOGENICITY AND WHOLE-GENOME SEQUENCING

As prespecified, immunogenicity analyses, which included analysis of antibodies to spike proteins and nucleocapsid proteins and neutralizing antibodies, were performed on serum samples obtained from participants in the substudy group during the trial to assess antibody titers and responses to SARS-CoV-2 antigens. Saliva specimens were collected at clinical sites or provided by trial participants at illness visits. Specimens positive for SARS-CoV-2 on RT-PCR testing were available for next-generation sequencing.

STATISTICAL ANALYSIS

The required number of symptomatic Covid-19 events for the primary analysis was approximately 150 and was reached after independent determination that the interim analysis criteria had been met. The cutoff date for the primary analysis was March 5, 2021. Adjudication of 14 outstanding potential cases that occurred before the cutoff date was conducted in parallel with the initial primary analysis. Once all events that occurred before the data cutoff had been fully adjudicated, the data analysis was refreshed and reflects the final data presented here. Data from participants whose treatment assignment was unmasked or from participants who received a Covid-19 vaccine administered under an emergency use authorization (EUA) were censored at the date of unblinding to the group assignment or EUA vaccine administration, whichever was earlier. All other participant data were censored at the date of the last trial contact. All deaths that were adjudicated as related to Covid-19 were included as a primary efficacy end-point event. Deaths that were adjudicated as not related to Covid-19 were treated as intercurrent events and therefore censored at the date of death.

The primary efficacy end point was a binary response, whereby a participant's status was classified as symptomatic Covid-19 or not, before the end of the follow-up period. We used a Poisson regression model with robust variance[7] adjusted for follow-up time as the primary efficacy analysis model to estimate the relative risk of the incidence of symptomatic infection in the AZD1222 group as compared with the placebo group. We calculated vaccine efficacy as 1 minus

the relative risk, with the result expressed as a percentage. The success criterion for the primary efficacy end point was statistical significance with an observed vaccine efficacy point estimate of at least 50%. A sensitivity analysis was performed with the use of a multiple imputation approach to evaluate the robustness of the analysis of the primary end point to missing data after censoring. Additional details on the statistical analyses are provided in the Supplementary Appendix.

RESULTS

TRIAL POPULATION

Between August 28, 2020, and January 15, 2021, a total of 34,117 unique participants were screened, 32,451 of whom met eligibility criteria and underwent randomization to receive the AZD1222 vaccine (21,635 participants) or placebo (10,816 participants) (Fig. 1). The majority of participants were men (55.6%) and had at least one coexisting condition (59.2%); the mean (±SD) age was 50.2±15.9 years (Table 1). Overall, 79.0% of the participants were White, 8.3% were Black, 4.4% were Asian, 4.0% were American Indian or Alaska Native, 2.4% were of multiple races or ethnic groups, 0.3% were Native Hawaiian or other Pacific Islander, and the remainder were of unknown or unreported race or ethnic group. Across both groups, 22.3% of participants were Hispanic or Latinx. Baseline demographic and clinical characteristics were balanced between the trial groups in both the safety analysis population (Table 1) and the fully vaccinated analysis population (Table S1 in the Supplementary Appendix). A total of 347 participants (1.6%) in the AZD1222 group and 169 (1.6%) in the placebo group were living with well-controlled human immunodeficiency virus infection.

SAFETY

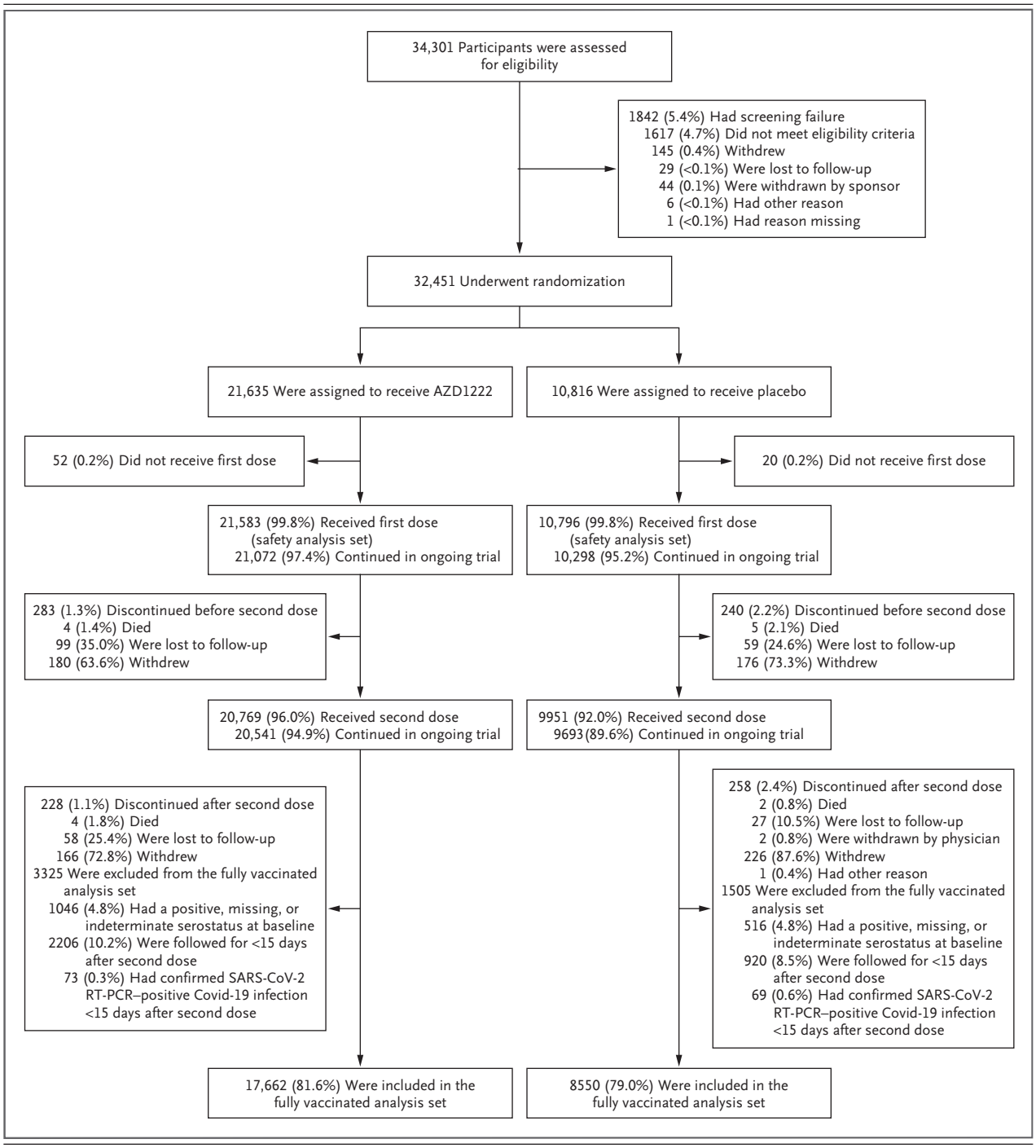
The incidence of adverse events is shown in Table S2. A total of 11,972 participants (37.0%) — 8771 (40.6%) in the AZD1222 group and 3201 (29.7%) in the placebo group — reported 23,538 adverse events. The most common adverse events, occurring in at least 5% of participants within 28 days after any dose in either group, were general pain (8.2% in the AZD1222 group and 2.3% in the placebo group), headache (6.2% and 4.6%, respectively), injection-site pain (6.8% and 2.0%), and fatigue (5.1% and 3.5%).

Figure 1 (facing page). Screening, Randomization, and Analyses.

Of the 34,301 persons initially screened, 184 were screened twice and counted twice. A total of 34,117 unique participants were screened for the trial; 181 persons failed screening twice and were counted twice, and 1661 unique participants failed screening, which does not include 4 persons who were screened and did not undergo randomization but are not included in the number of failed screenings. Of the total 32,451 participants who underwent randomization, 1 participant was enrolled at two separate sites under two subject identification numbers, underwent randomization at both sites, and received both doses of assigned vaccine or placebo. This participant is included once in the all-participants analysis population but is excluded from all other analysis populations. Three participants underwent randomization twice in error. The safety analysis population for each group reflects treatment actually received. The number of participants in each group who received the second dose are those included as of data cutoff. Participants could be excluded from the fully vaccinated analysis population for more than one reason, including for not receiving two doses, and may therefore be counted for exclusion twice. Group assignment was unblinded for 7635 participants (35.3%) in the AZD1222 group and 4157 participants (38.4%) in the placebo group after the second dose. Covid-19 denotes coronavirus disease 2019, RT-PCR reverse transcriptase–polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

A similar percentage of participants in each group had a serious adverse event within 28 days after any dose: 119 serious adverse events occurred among 101 participants (0.5%) in the AZD1222 group and 59 events among 53 participants (0.5%) in the placebo group. During the entire trial period, a total of 7 adverse events leading to death occurred in 7 participants in the AZD1222 group, and 9 adverse events leading to 7 deaths occurred in the placebo group. These deaths are described in Table S2. No deaths were considered by investigators to be related to the vaccine or placebo. No deaths related to Covid-19 occurred in the AZD1222 group, and two deaths related to Covid-19 occurred in the placebo group.

Medically attended adverse events and adverse events of special interest within 28 days after a dose also occurred in similar proportions in the two groups (Table S2). The incidences of individual adverse events related to the vaccine or placebo during the entire trial period are shown in Tables S3 through S5. The incidence of potential immune-mediated conditions was similar in



the two groups (1.8% in the AZD1222 group and 3.4% in the placebo group), as were the incidences of adverse events of special interest: neurologic (0.5% in the AZD1222 group and 0.4% in the placebo group), vascular (0.1% in the AZD1222 group and <0.1% in the placebo group), and hematologic (<0.1% in both groups). Specifically, the incidences of deep-vein thrombosis (<0.1% in both groups), pulmonary embolism (<0.1% in both groups), thrombocytopenia (<0.1% in the AZD1222 group and none in the placebo group), and immune thrombocytopenia (none in the AZD1222 group and <0.1% in the placebo group) were low and similar in the groups. There were no cases in either group of thrombosis with thrombocytopenia, cerebral

Table 1. Demographic and Clinical Characteristics of the Safety Population at Baseline.*

Characteristic	AZD1222 (N=21,587)	Placebo (N=10,792)	Total (N=32,379)
Follow-up time from second dose — days†			
Mean	64.8±21.4	64.9±21.7	NA
Median	61.0	61.0	NA
Range	1–129	1–129	NA
Age — yr‡			
Mean	50.2±15.9	50.2±15.9	50.2±15.9
Median	51.0	51.0	51.0
Range	18–100	18–92	18–100
Age group — no. (%)			
≥18 to 64 yr	16,760 (77.6)	8381 (77.7)	25,141 (77.6)
≥65 yr	4827 (22.4)	2411 (22.3)	7238 (22.4)
Sex — no. (%)			
Male	12,012 (55.6)	6003 (55.6)	18,015 (55.6)
Female	9575 (44.4)	4789 (44.4)	14,364 (44.4)
Hispanic or Latinx ethnic group — no. (%)§			
No	16,470 (76.3)	8200 (76.0)	24,670 (76.2)
Yes	4771 (22.1)	2452 (22.7)	7223 (22.3)
Not reported	296 (1.4)	125 (1.2)	421 (1.3)
Unknown	50 (0.2)	15 (0.1)	65 (0.2)
Race or ethnic group — no. (%)§			
White	17,061 (79.0)	8522 (79.0)	25,583 (79.0)
Black	1794 (8.3)	892 (8.3)	2686 (8.3)
Asian	947 (4.4)	481 (4.5)	1428 (4.4)
American Indian or Alaska Native	851 (3.9)	429 (4.0)	1280 (4.0)
Multiple	510 (2.4)	256 (2.4)	766 (2.4)
Native Hawaiian or other Pacific Islander	61 (0.3)	21 (0.2)	82 (0.3)
Not reported	262 (1.2)	137 (1.3)	399 (1.2)
Unknown	101 (0.5)	54 (0.5)	155 (0.5)
Country — no. (%)			
United States	19,145 (88.7)	9572 (88.7)	28,717 (88.7)
Chile	1470 (6.8)	729 (6.8)	2199 (6.8)
Peru	972 (4.5)	491 (4.5)	1463 (4.5)
SARS-CoV-2 serostatus — no. (%)¶			
Negative	20,593 (95.4)	10,296 (95.4)	30,889 (95.4)
Positive	623 (2.9)	292 (2.7)	915 (2.8)
Indeterminate	0	0	0
Missing data	117 (0.5)	60 (0.6)	177 (0.5)
Not performed	254 (1.2)	144 (1.3)	398 (1.2)
Coexisting conditions — no./total no. (%)‖			
Any coexisting condition at baseline	12,753/21,585 (59.1)	6426/10,790 (59.6)	19,179/32,375 (59.2)
History of obesity**	5808/21,585 (26.9)	3011/10,790 (27.9)	8819/32,375 (27.2)

Table 1. (Continued.)

Characteristic	AZD1222 (N=21,587)	Placebo (N=10,792)	Total (N=32,379)
High blood pressure	5851/21,585 (27.1)	2890/10,790 (26.8)	8741/32,375 (27.0)
History of smoking	4004/21,585 (18.5)	1991/10,790 (18.5)	5995/32,375 (18.5)
Asthma	2142/21,585 (9.9)	1140/10,790 (10.6)	3282/32,375 (10.1)
Type 2 diabetes	1538/21,585 (7.1)	857/10,790 (7.9)	2395/32,375 (7.4)
Serious heart conditions	737/21,585 (3.4)	346/10,790 (3.2)	1083/32,375 (3.3)
Liver disease	341/21,585 (1.6)	179/10,790 (1.7)	520/32,375 (1.6)
COPD	297/21,585 (1.4)	171/10,789 (1.6)	468/32,374 (1.4)
Cerebrovascular diseases	224/21,585 (1.0)	114/10,790 (1.1)	338/32,375 (1.0)
Chronic kidney disease	166/21,585 (0.8)	58/10,790 (0.5)	224/32,375 (0.7)
Type 1 diabetes	122/21,585 (0.6)	71/10,790 (0.7)	193/32,375 (0.6)
Thalassemia	34/21,585 (0.2)	21/10,789 (0.2)	55/32,374 (0.2)
Scarring in the lungs: pulmonary fibrosis	33/21,585 (0.2)	12/10,790 (0.1)	45/32,375 (0.1)
Dementia	7/21,585 (<0.1)	8/10,790 (<0.1)	15/32,375 (<0.1)
Sickle cell disease	8/21,585 (<0.1)	7/10,790 (<0.1)	15/32,375 (<0.1)
Lower immune health due to solid organ transplantation	5/21,584 (<0.1)	4/10,790 (<0.1)	9/32,374 (<0.1)
Cystic fibrosis	1/21,585 (<0.1)	1/10,790 (<0.1)	2/32,375 (<0.1)
Medical history — no. (%)			
HIV infection	347 (1.6)	169 (1.6)	516 (1.6)
Cancer	1398 (6.5)	692 (6.4)	2090 (6.5)

* Plus–minus values are means ±SD. Data shown are from the safety analysis population. Numbers are based on vaccine or placebo actually received. COPD denotes chronic obstructive pulmonary disease, HIV human immunodeficiency virus, NA not available, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Uncensored data are shown from the full analysis population, from the second dose to the end of the trial. Data were available for 20,773 participants in the AZD1222 group and 9947 participants in the placebo group.
‡ Age reflects the age at the date of signed informed consent.
§ Race and ethnic group were reported by the participant. The same questions and categories used to determine participant race and ethnic group were used for all countries and sites. American Indian includes participants who indicated they were South American and participants who were indigenous to Peru. Multiple includes participants who reported that they were of more than one race.
¶ Serostatus at baseline was defined by the nucleocapsid antibody level as measured by the Elecsys Anti-SARS-CoV-2 serology test (Roche).
‖ Percentages for coexisting conditions were calculated on the basis of participants with available data.
** Obesity is a body-mass index (the weight in kilograms divided by the square of the height in meters) greater than 30.

venous sinus thrombosis, or venous thrombosis in unusual locations.

REACTOGENICITY

In the substudy population, more participants in the AZD1222 group than in the placebo group had local solicited adverse events (74.1% in the AZD1222 group vs. 24.4% in the placebo group) and systemic solicited adverse events (71.6% vs. 53.0%) (Fig. 2). The majority of solicited adverse events (92.6%) across both groups were mild or moderate in intensity. Events occurred less frequently after the second dose than after the first dose in both age groups, a difference that was more marked in participants 18 to 64 years of age. The majority of local and systemic solicited adverse events resolved within 1 to 2 days after onset.

EFFICACY

Once adjudication of all events that occurred before the data cutoff was complete, 203 symptomatic Covid-19 events met the case definition of the primary end point and were included in the updated primary analysis for the fully vaccinated analysis population (17,662 participants

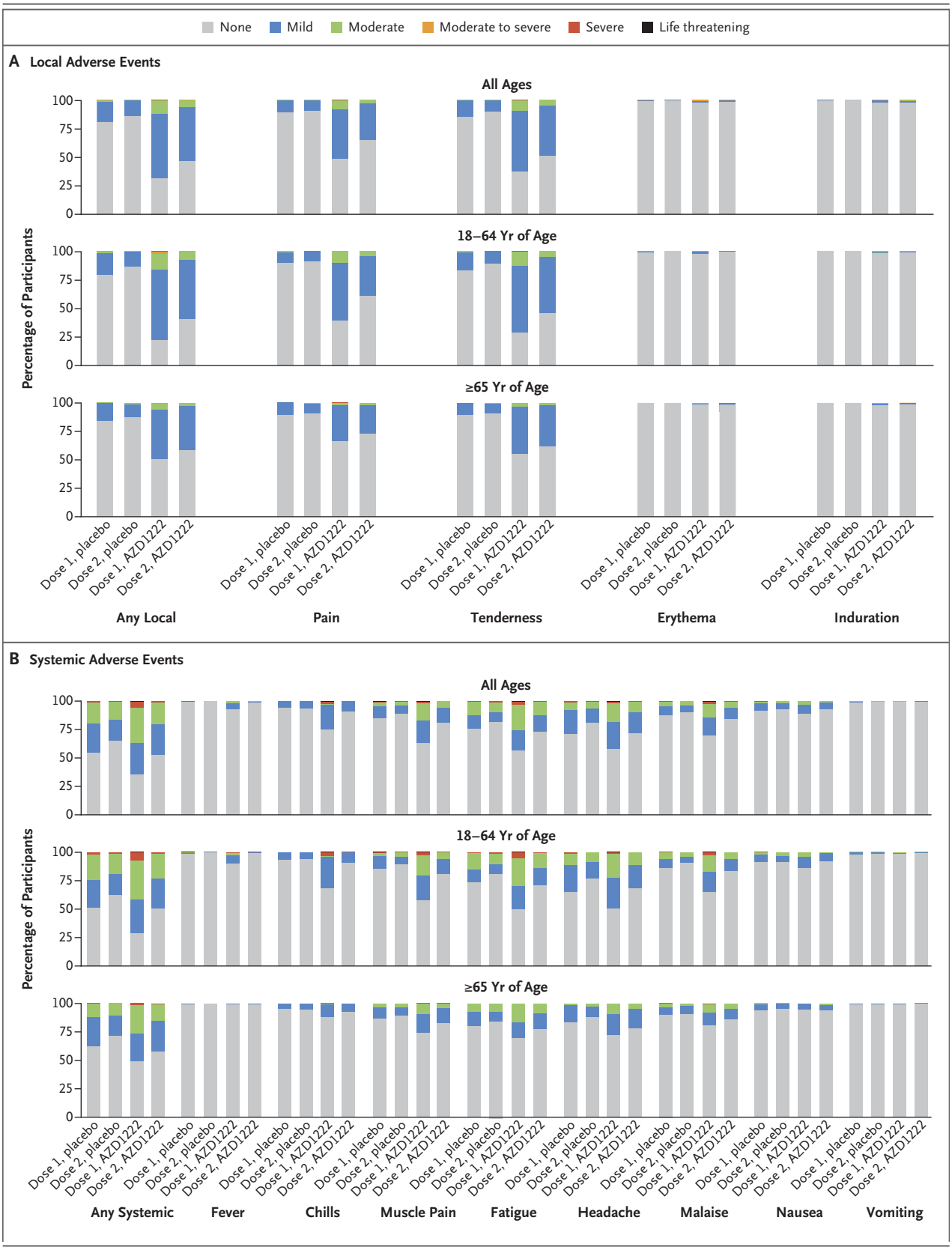


Figure 2 (facing page). Local and Systemic Solicited Adverse Events after First and Second Dose, by Age Group.

Erythema and induration were classified by size as mild (2.5 to 5 cm), moderate (5.1 to 6 cm), or moderate-to-severe (>6 cm). Fevers were graded by temperature as none (≤37.8°C), mild (37.9 to 38.4°C), moderate (38.5 to 38.9°C), severe (39.0 to 40.0°C), or life threatening (≥40.1°C). The most common solicited adverse events that occurred in at least 5% of participants within 7 days after any dose in either group were tenderness (68.4% in the AZD1222 group and 19.0% in the placebo group) and pain (58.3% and 15.7%), both local adverse events; the most common systemic adverse events were headache (50.2% in the AZD1222 group and 35.5% in the placebo group), fatigue (49.7% and 31.2%), muscle pain (41.9% and 19.5%), malaise (35.0% and 17.0%), chills (28.2% and 9.5%), nausea (15.3% and 12.1%), and temperature higher than 37.8°C (7.0% and 0.6%). The All Ages group included 1013 participants for dose 1, placebo; 968 for dose 2, placebo; 2037 for dose 1, AZD1222; and 1962 for dose 2, AZD1222. The age 18 to 64 group included 663 participants for dose 1, placebo; 629 for dose 2, placebo; 1339 for dose 1, AZD1222; and 1288 for dose 2, AZD1222. The age 65 and older group included 350 participants for dose 1, placebo; 339 for dose 2, placebo; 698 for dose 1, AZD1222; and 674 for dose 2, AZD1222.

in the AZD1222 group and 8550 in the placebo group) (Fig. 1). The efficacy analyses presented here are based on the updated primary analysis of the group whose data were censored as of the cutoff date. In the full analysis population, the median follow-up duration from the second dose to the data cutoff date, regardless of unblinding of group assignments, was 61.0 days (range, 1 to 129) in both groups (Table 1). Overall, 73 events (0.4%) occurred in the AZD1222 group and 130 (1.5%) occurred in the placebo group (Fig. 3). For the primary efficacy end point, the success criterion was met in the fully vaccinated analysis population on the basis of an overall vaccine efficacy estimate of 74.0% (95% confidence interval [CI], 65.3 to 80.5; P<0.001). Results regarding the cumulative incidence of the first SARS-CoV-2 RT-PCR–positive symptomatic illness after the second dose of AZD1222 (Fig. 4) showed that the effect of AZD1222 began soon after the second dose. Vaccine efficacy was consistent in the analyses in which follow-up data were not censored at unblinding of the treatment assignment or EUA vaccination (74.3%; 95% CI, 66.0 to 80.6) and also when multiple imputation was used (73.3%; 95% CI, 64.6 to 79.9).

On September 9, 2020, the trial was placed on clinical hold owing to an event of transverse myelitis reported in a different AZD1222 clinical study.[2] After a review of the event and all available safety data, the Food and Drug Administration lifted the clinical hold on October 23, 2020, and the trial resumed on October 28, 2020. A total of 775 participants (2.4%) in the safety analysis population were affected by the clinical hold and received their second dose outside the planned 28-day window. Vaccine efficacy in this subgroup of participants who received their second dose at an extended dosing interval was consistent with that in the overall group (78.1%; 95% CI, 49.2 to 90.6).

Vaccine efficacy estimates according to subgroup are shown in Figure 3, although small case numbers hindered confidence in some subgroup estimates, such as those for ICU admissions and those based on data from participants in Chile and Peru. Estimated vaccine efficacy was high against symptomatic illness in participants 18 to 64 years of age (72.8%; 95% CI, 63.4 to 79.9) and those 65 years of age or older (83.5%; 95% CI, 54.2 to 94.1) and was consistent across participants of different races and ethnic groups, status with respect to coexisting conditions, baseline SARS-CoV-2 serostatus, and sex. In Chile, 4 cases of symptomatic illness were noted among 1360 participants in the AZD1222 group as compared with 2 cases among 672 participants in the placebo group. In Peru, 11 cases among 867 participants in the AZD1222 group and 9 cases among 435 participants in the placebo group were observed. Estimated vaccine efficacy against symptomatic Covid-19 regardless of evidence of previous SARS-CoV-2 infection (a secondary end point) was 73.7% (95% CI, 65.1 to 80.1; P<0.001).

The vaccine was significantly effective against all other key secondary efficacy end points (Fig. 3). In the fully vaccinated analysis population, no cases of severe or critical symptomatic Covid-19 were observed among the 17,662 participants in the AZD1222 group, as compared with 8 cases (<0.1%) among the 8550 participants in the placebo group. Estimated vaccine efficacy of AZD1222 for the prevention of Covid-19 (as defined by CDC criteria) was high (69.7%; 95% CI, 60.7 to 76.6; P<0.001), as was efficacy against emergency department visits attributed to Covid-19 (94.8%; 95% CI, 59.0 to 99.3; P=0.005),

with 1 (<0.1%) emergency department visit in the AZD1222 group and 9 (0.1%) in the placebo group. Estimated vaccine efficacy against Covid-19–related hospitalizations (an exploratory end point) was 94.2% (95% CI, 53.3 to 99.3) (Fig. 3). One participant in the AZD1222 group who had a Covid-19–related emergency department visit had an allergic reaction to a monoclonal antibody treatment and was hospitalized. This hospitalization did not meet the criteria for severe or critical Covid-19.

The estimated vaccine efficacy for incidences of first SARS-CoV-2 RT-PCR–positive symptomatic illness occurring after the first dose of AZD1222 or placebo is described in Figure S1. AZD1222 was efficacious at preventing infection with SARS-CoV-2, as measured by nucleocapsid antibody seroconversion 15 days or more after the second dose; this included all participants who tested positive for SARS-CoV-2 nucleocapsid antibodies regardless of symptoms or severity (64.3%; 95% CI, 56.1 to 71.0; P<0.001). Additional details of the efficacy analyses are provided in the Supplementary Appendix.

HUMORAL IMMUNOGENICITY

Participants who received AZD1222 and were seronegative at baseline showed strong vaccine-induced serum IgG responses to the spike protein (Fig. S2). Levels of neutralizing antibodies were higher than baseline at all time points in the AZD1222 group, increasing further after a second dose, but remained low throughout the trial in the placebo group (Fig. S3).

WHOLE-GENOME SEQUENCING OF SARS-COV-2 SAMPLES

Among participants in the full analysis population (the 30,889 participants who were seronegative at baseline), whole-genome sequencing of saliva samples obtained from 176 participants in the AZD1222 group and 183 participants in the placebo group attending illness visits, regardless of qualifying symptoms, yielded four cases of variants of concern, including alpha and beta variants (one putative B.1.351 case was determined by clade). Of the variants of interest observed, epsilon was the most common (B.1.429 in 14 participants and B.1.427 in 3 participants) followed by iota (B.1.526 in 1 participant) (Table S6).

DISCUSSION

AZD1222 is a safe and efficacious vaccine for the prevention of symptomatic Covid-19. In a diverse adult population of more than 32,000 participants, two doses of AZD1222 administered 4 weeks apart were 74% efficacious overall at preventing symptomatic illness 15 days or more after the second dose.

Success criteria for AZD1222 were met on the basis of the measured primary and secondary end points. When measured according to the CDC definition of Covid-19, which can include mild disease, AZD1222 had 70% efficacy. Furthermore, although event rates were low, participants who received AZD1222 had no cases of severe or critical symptomatic Covid-19 and had significantly fewer Covid-19–related emergency department visits, hospitalizations, and ICU admissions than participants who received placebo.

A key strength of this trial is that it showed the efficacy of AZD1222 across all age groups, including in adults 65 years of age or older. This finding is further supported by emerging real-world data from the United Kingdom that show high vaccine effectiveness for prevention of Covid-19, including severe disease and hospitalization in older adults, after the first AZD1222 dose.[8-10]

Because of small case numbers in Chile and Peru, we were unable to precisely estimate vaccine efficacy in those groups. This trial was not designed to assess vaccine efficacy according to enrollment country or in smaller subpopulations.

Although the level of SARS-CoV-2 neutralizing antibodies that correlates with protection is not yet known, the role of these antibodies as an important contributor to protective immunity is widely accepted.[11] In our trial, both SARS-CoV-2 spike protein binding and neutralizing antibodies increased in all age groups after the first dose of AZD1222 and further increased from baseline when measured 28 days after the second dose,[1] a finding consistent with results from previous trials.[12]

No new vaccine-related safety signals were identified, and solicited adverse events were mostly mild or moderate and were fewer in number after the second dose of AZD1222 than after the first. Results from this trial showed no evidence of increased overall risk of neurologic events,

Efficacy End Point	AZD1222	Placebo	Vaccine Efficacy	P Value
	no. of events/total no. (%)		*% (95% or 97.5% CI)*	
Primary: symptomatic Covid-19				
Overall	73/17,662 (0.4)	130/8550 (1.5)	74.0 (65.3 to 80.5)	<0.001
Age				
≥18 to 64 yr	68/13,966 (0.5)	116/6738 (1.7)	72.8 (63.4 to 79.9)	NA
≥65 yr	5/3696 (0.1)	14/1812 (0.8)	83.5 (54.2 to 94.1)	NA
Race or ethnic group				
Black	2/1401 (0.1)	12/706 (1.7)	91.8 (63.4 to 98.2)	NA
White	58/14,011 (0.4)	99/6755 (1.5)	73.1 (62.8 to 80.5)	NA
American Indian or Alaska Native	9/744 (1.2)	9/373 (2.4)	50.1 (–25.7 to 80.2)	NA
Other	4/1506 (0.3)	10/716 (1.4)	81.6 (41.2 to 94.2)	NA
Hispanic or Latinx ethnic group				
Yes	26/4035 (0.6)	30/2064 (1.5)	57.5 (28.2 to 74.8)	NA
No	45/13,351 (0.3)	98/6370 (1.5)	79.0 (70.1 to 85.3)	NA
Sex				
Male	41/9922 (0.4)	84/4829 (1.7)	77.2 (66.9 to 84.3)	NA
Female	32/7740 (0.4)	46/3721 (1.2)	68.2 (50.0 to 79.7)	NA
SARS-CoV-2 baseline serostatus				
Negative	73/17,662 (0.4)	130/8550 (1.5)	72.9 (63.6 to 79.9)	NA
Positive	0/543	1/253 (0.4)	100.0 (–1760.3 to NE)	NA
Enrollment country				
United States	58/15,435 (0.4)	119/7443 (1.6)	77.5 (69.2 to 83.6)	NA
Chile	4/1360 (0.3)	2/672 (0.3)	6.7 (–409.3 to 82.9)	NA
Peru	11/867 (1.3)	9/435 (2.1)	38.5 (–48.2 to 74.5)	NA
Covid-19 coexisting condition				
≥1	43/10,376 (0.4)	82/5105 (1.6)	75.2 (64.2 to 82.9)	NA
None	30/7285 (0.4)	48/3444 (1.4)	71.8 (55.5 to 82.1)	NA
Secondary end points: overall				
Symptomatic Covid-19 regardless of evidence of previous SARS-CoV-2 infection	76/18,563 (0.4)	135/9031 (1.5)	73.7 (65.1 to 80.1)	<0.001
Symptomatic Covid-19 according to CDC criteria	95/17,662 (0.5)	145/8550 (1.7)	69.7 (60.7 to 76.6)	NA
Severe or critical symptomatic Covid-19	0/17,662	8/8550 (<0.1)	100.0 (71.6 to NE)	<0.001
Covid-19–related emergency department visits	1/17,662 (<0.1)	9/8550 (0.1)	94.8 (59.0 to 99.3)	0.005
First response	156/17,662 (0.9)	202/8550 (2.4)	64.3 (56.1 to 71.0)	<0.001
Exploratory end points: overall				
Covid-19–related hospitalizations	1/17,662 (<0.1)	8/8550 (<0.1)	94.2 (53.3 to 99.3)	NA
Covid-19–related ICU admissions	0/17,662	1/8550 (<0.1)	100.0 (–1781.6 to NE)	NA

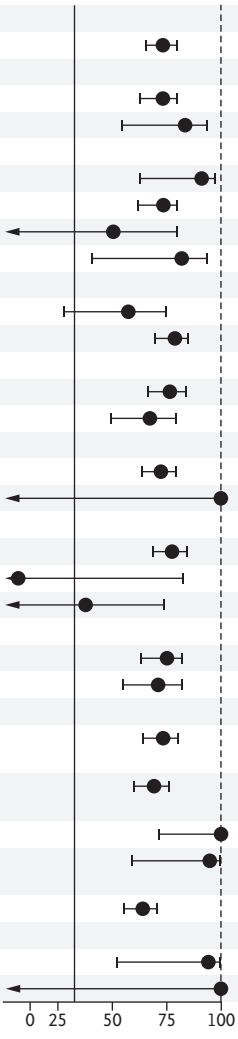
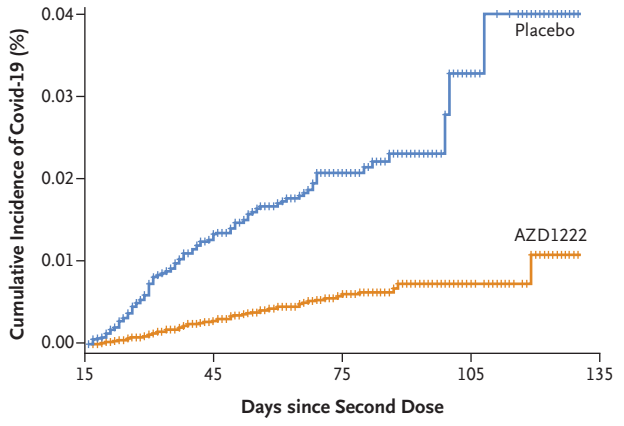


Figure 3. Estimated Vaccine Efficacy ≥15 Days after the Second Dose (Fully Vaccinated Analysis Population).

Values shown for no. of events/total no. are the number of events that occurred among the participants within each group and do not account for censoring due to unblinding of group assignment or loss to follow-up. The primary efficacy end point is the first case of SARS-CoV-2 RT-PCR–positive symptomatic illness occurring 15 days or more after the second dose of AZD1222 or placebo among participants with negative serostatus at baseline. Vaccine efficacy is shown with 95% confidence intervals (CIs), except for vaccine efficacy values for the primary efficacy end point according to SARS-CoV-2 baseline serostatus, the secondary end point of severe or critical symptomatic Covid-19, and the exploratory end point of Covid-19–related intensive care unit (ICU) admissions, which are based on a one-sided 97.5% CI calculated with the exact Poisson model, owing to nonconvergence of the Poisson regression with robust variance. Race and ethnic group were reported by the participant. Other denotes participants who provided a race or ethnic group identification other than White, Black, or American Indian or Alaska Native. Key secondary end points were incidence of symptomatic illness (at 15 days or more after the second dose of AZD1222 or placebo) regardless of evidence of previous SARS-CoV-2 infection at baseline, severe or critical symptomatic Covid-19 (at 15 days or more after the second dose of AZD1222 or placebo), Covid-19-related emergency department visits, symptomatic Covid-19 as defined by Centers for Disease Control and Prevention (CDC) criteria, and first response (change from negative serostatus for SARS-CoV-2 nucleocapsid antibodies at baseline to positive serostatus after receiving AZD1222 or placebo). P values are reported for the primary and key secondary outcomes; analyses followed prespecified plan to adjust for multiple comparisons. I bars indicate confidence intervals; arrows indicate truncated values, with actual values shown in the accompanying column; the dashed vertical line represents the upper limit (i.e., 100% vaccine efficacy); and the solid vertical line represents the nominally statistically significant criterion of a lower confidence interval greater than 30% applicable to the primary end point and is shown for reference. NA denotes not available, and NE could not be estimated.



No. at Risk

Placebo	8,550	5,644	1983	142
AZD1222	17,662	12,210	4545	316

Figure 4. Time to First SARS-CoV-2 RT-PCR–Positive Symptomatic Illness Occurring 15 Days or More after the Second Dose (Fully Vaccinated Analysis Population).

The time to the first event was relative to the time of the actual second dose administration, calculated as (date of SARS-CoV-2–positive test) − (date of second dose of AZD1222 or placebo + 14 days) + 1. For participants whose data were censored, the censoring time was from the date of the second dose of AZD1222 or placebo + 14 days to the last time observed before data cutoff (March 5, 2021). The cumulative incidence of Covid-19 was estimated with the Kaplan–Meier method. Vaccine efficacy, estimated on the basis of the supportive analysis of the time to primary efficacy end point with the use of the Cox proportional-hazards model, with the randomization and age groups at the time of informed consent as covariates, was 73.9% (95% CI, 65.3 to 80.5). Tick marks indicate censored data.

specifically demyelinating disease or acute transverse myelitis, with AZD1222 as compared with placebo and showed no instances of enhanced respiratory disease.

In multiple countries, rare instances of thrombotic events with thrombocytopenia have been reported after Covid-19 vaccinations,[13-15] including among persons who received AZD1222.[16-21] Although no evidence of increased overall risk of thrombosis or thrombosis with thrombocytopenia was noted among participants who received AZD1222 in this trial, thrombosis with thrombocytopenia syndrome (also known as vaccine-induced immune thrombotic thrombocytopenia) is rare. Independent safety reviews by regulatory authorities of available clinical and real-world evidence[2,3,8,9,22,23] have concluded that the benefits of AZD1222 outweigh the potential risks, with protection from the serious consequences of Covid-19 increasing with age and SARS-CoV-2 infection rate.[17,24,25]

A comparison of data from different trials, including trials that evaluated the same vaccine, is challenging owing to numerous variables, such as difference in trial participants, symptomatic illness criteria, and circulating viruses.[26] With dosing intervals ranging from 4 weeks, as reported here, to 12 weeks, as reported previously, AZD1222 has shown similar safety, side-effect profile, efficacy, and immunogenicity in adults in a pooled analysis of trials across different geographic locations,[1,2] albeit with lower efficacy observed against mild-to-moderate disease in South Africa associated with the beta (B.1.351) variant.[27]

A limitation of this trial is the early unblinding of group assignment for more than one third of participants, whose data were censored for most analyses. Unblinding occurred because other Covid-19 vaccines became authorized for use during the trial, allowing participants to make individual vaccination decisions. Other limitations include the small number of variants of concern owing to the timing of the trial within the pandemic and the short duration of follow-up, which also precludes evaluations of the duration of the efficacy and long-term safety of AZD1222. Analysis of the efficacy of the vaccine over time is ongoing. These data support AZD1222 as a safe and efficacious vaccine that prevents symptomatic and severe Covid-19 across diverse adult populations.

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med. DOI: 10.1056/NEJMoa2105290

Supplementary Appendix

Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 Vaccine

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SUPPLEMENTARY METHODS

Trial Oversight

Training and certification were required for all site personnel responsible for completing assessments. A Protocol Safety Review team and an Independent Data Safety Monitoring Board reviewed safety data throughout the trial and potential Covid-19 cases were assessed by an independent adjudication committee that was unaware of group assignment. AstraZeneca was involved in trial design, collection, analysis, and interpretation of the data. Input was also obtained from the Biomedical Advanced Research and Development Authority, the National Institute of Allergy and Infectious Diseases, the National Institute of Health, the Covid-19 Prevention Network, and the trial Co-Chairs. Authors Ann Falsey and Magdalena Sobieszczyk developed the first manuscript draft with medical writing assistance funded by AstraZeneca.

Trial Definitions

Term	Definition
Increased risk of SARS-CoV-2 infection	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)
Medically stable	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
Clinical signs at rest indicative of severe systemic illness	Respiratory rate 30 or more breaths per minute; heart rate 125 or more beats per minute; oxygen saturation 93% or less on room air at sea level; or partial pressure of oxygen to fraction of inspired oxygen ratio less than 300 mmHg
Respiratory failure	Defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation
Evidence of shock	Systolic blood pressure less than 90 mmHg, diastolic blood pressure less than 60 mmHg, or requiring vasopressors
MAAEs	MAAEs were defined as AEs leading to medically-attended visits that were not routine visits for physical examination, vaccination, or illness visits such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel for any reason

AESIs	AESIs included terms identified by the Brighton Collaboration involving events associated with vaccination in general[1]

AE, adverse events; AESIs, adverse events of special interest; Covid-19, coronavirus disease 2019; MAAEs, medically-attended adverse events; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Full Trial Inclusion and Exclusion Criteria

Full inclusion criteria were:

- Adult, 18 years of age or older at the time of consent
- Increased risk of SARS-CoV-2 infection (see **Definitions**)
- Medically stable (see **Definitions**) such that, according to the judgment of the investigator, hospitalization within the trial period was not anticipated and the participant appeared likely to be able to remain in the trial through the end of protocol-specified follow-up
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
- Women of childbearing potential were required to:
    - Have a negative pregnancy test on the day of screening and on Day 1
    - Use one highly effective form of birth control for at least 28 days prior to Day 1 and agree to continue using one highly effective form of birth control through 60 days following administration of the second dose of trial intervention.
- 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 postmenopausal
- Capable of giving signed informed consent (or legally authorized representative able to provide consent)

Full exclusion criteria were:

- History of allergy to any component of the vaccine
- History of Guillain-Barré syndrome or any other demyelinating condition
- Significant infection or other acute illness, including fever over 100°F (over 37°C) on the day prior to or day of randomization

- History of laboratory-confirmed SARS-CoV-2 infection
- Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia
- Recurrent severe infections and use of immunosuppressant medication within the past 6 months (20 mg/kg/day or more of prednisone or its equivalent, given daily or on alternate days for 15 days or more within 30 days prior to administration of trial intervention). The following exceptions were permitted:
    - Topical/inhaled steroids or short-term oral steroids (course lasting 14 days or less)
    - Human immunodeficiency virus-positive stable participants on stable antiretroviral therapy
- History of primary malignancy except for:
    - 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
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated uterine cervical carcinoma in situ without evidence of disease
    - Localized prostate cancer
- Clinically significant bleeding disorder (for example, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venipuncture
- 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 coexisting conditions are allowed)
- Any other significant disease, disorder, or finding that may have significantly increased the risk to the participant because of participation in the trial, affect the ability of the participant to participate in the trial, or impair interpretation of the trial data

- Receipt of, or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or Covid-19
    - For participants who became hospitalized with Covid-19, receipt of licensed treatment options and/or participation in investigational treatment studies was permitted
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of trial intervention
- Receipt of immunoglobulins and/or any blood products within 3 months prior to administration of trial intervention or expected receipt during the period of trial follow-up
- Involvement in the planning and/or conduct of this trial (applied to both Sponsor staff and/or staff at the trial site)
- For women only: pregnancy (confirmed with positive pregnancy test) or breastfeeding
- Had donated 450 mL or more of blood products within 30 days prior to randomization or expected to donate within 90 days of administration of second dose of trial intervention

Participant lifestyle considerations were:

- Participants were required to follow the contraception requirements as defined in the inclusion criteria
- Concomitant medications or vaccines (including over-the-counter or prescription medicines and excluding vitamins and/or herbal supplements) received by the participants at the time of enrollment or during the trial were recorded
- If diagnosed with Covid-19, participants were required to wear a biosensor, digital health device to continuously track biophysical parameters

Trial Design

For the primary endpoint, symptomatic was defined as 1 or more of the following criteria: pneumonia diagnosed by chest X-ray or computed tomography scan; oxygen saturation 94% or less on room air or requiring new initiation or escalation in supplemental oxygen; or new or worsening dyspnea/shortness of breath; or 2 or more of the following symptoms/signs: fever over 100°F or feverishness; new or worsening cough; myalgia/muscle pain; fatigue that interferes with activities of daily living; vomiting and/or diarrhea (one finding counted

toward endpoint definition); or anosmia and/or ageusia (one finding counted toward endpoint definition).

Participants who experienced 1 or more of the following Covid-19 qualifying symptoms were to contact the trial team:

Covid-19 Qualifying Symptoms*

Duration	**Symptom**
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
Present for 2 days or more	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhea

*Adapted from Centers for Disease Control and Prevention (CDC) 2020.

Trial Illness and Sampling Procedures

If a participant presented with Covid-19 qualifying symptom(s) on Days 1–3 post-vaccination, the nasal pharyngeal (NP) swab that was collected on Day 1 was sent for local SARS-CoV-2 RT-PCR testing. If positive, the participant was instructed to initiate illness visits. If negative, the participant continued with scheduled assessments. After Day 3 post-vaccination, a participant with Covid-19 qualifying symptoms was instructed to attend illness visit 1 where two NP swabs were collected, one for local RT-PCR testing and one for central testing. The local test was used for patient management and the central test was used to determine SARS-CoV-2 RT-PCR status. If the local RT-PCR was negative, the participant was directed to stop illness visits and resume regular follow-up visits. If positive, the participant continued with illness visits and was instructed in home collection requirements, including use of a digital health device, saliva samples, and e-Diary recordings. NP swabs for central lab RT-PCR were also collected at illness visits on Days 14, 21, and 28. In the event that the central lab PCR was not collected or was not available (i.e., lost in shipping, spoiled, etc.) then the local lab PCR result was used for endpoint determination. If the local and central PCR test results were discordant, such that the local was positive and the central was negative, the adjudication committee could consult the saliva RT-PCR result in determining whether the participant was PCR-positive.

Serum samples were collected from participants at Days 1, 29, 57, 90, 180, 360, and 730 for SARS-CoV-2 antibody testing to monitor participants for interim acquisition of asymptomatic infection. Authorized laboratories assessed serologic responses to AZD1222 by the rate of participants seroconverting from negative to positive as defined by a validated immunoassay directed at the SARS-CoV-2 spike antigen. Additional serum samples were collected in the substudy at Days 15 and 43 for immunogenicity testing. Saliva was collected during illness visits and at home to quantify duration of viral shedding on Days 1, 3, 5, 8, 11, 14, 21, and 28 of the illness.

Severe or Critical Symptomatic Covid-19

For this trial, severe or critical symptomatic Covid-19 was defined as laboratory-confirmed SARS-CoV-2 RT-PCR–positive symptomatic illness plus 1 or more of the following features: clinical signs at rest indicative of severe systemic illness; respiratory failure;

evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; ICU admission; or death.

Humoral Immunogenicity and Whole Genome Sequencing

SARS-CoV-2 Antigen Testing Assays

SARS-CoV-2 nucleocapsid antibodies were measured for all participants with a validated Roche Elecsys® Anti-SARS-CoV-2 nucleocapsid serology test (Covance CLS, Indianapolis, IN). A validated quantitative multiplexed electrochemiluminescent assay was used to determine responses to the spike, receptor-binding domain, and nucleocapsid SARS-CoV-2 viral antigens (PPD Vaccines, Richmond, VA). Antibody concentrations were determined in an indirect binding format on a 10-spot plate on the Meso Scale Discovery® platform. A reference standard was created by pooling pre-screened Covid-19–positive human serum samples. Test sample antibody concentrations were determined by interpolating relative light units to a standard curve generated from the serially diluted reference standard and assigned a concentration in arbitrary units (AU)/mL. Validation included precision and ruggedness, dilutional linearity, selectivity, and relative accuracy for each SARS-CoV-2 antigen.

Validated Pseudovirus Neutralization Assay

Neutralizing antibodies were assessed in a validated lentivirus-based SARS-CoV-2 pseudovirus assay (Monogram Biosciences, South San Francisco, CA). Pseudovirions containing luciferase and a Wuhan-Hu-1 spike protein were preincubated with serial dilutions of serum. Antibody titers are reported as the reciprocal of the serum dilution conferring 50% inhibition (ID_{50}) of pseudovirus infection. A specificity control containing a non-specific pseudovirus (for example, Avian Influenza envelope) was utilized to determine activity was specific to SARS-CoV-2. Method validation included accuracy, repeatability, intermediate precision, and linearity.

Whole Genome Sequencing of SARS-CoV-2 Samples

Saliva specimens were collected at clinical sites or self-collected by trial participants in Spectrum Solutions SDNA-1000 Saliva Collection Device. Saliva specimens that were assessed as positive by the TaqPath™ SARS-CoV-2 Assay (Infinity BiologiX, Piscataway, NJ) were available for next-generation sequencing by the Illumina COVIDseq Test. The first

positive specimen for each trial participant for whom a positive saliva shedding sample was available was assessed.

The analysis workflow included steps for viral RNA extraction, RNA-to-cDNA conversion, PCR, library preparation, sequencing, analysis, and report generation. RNA extraction was performed using the PerkinElmer chemagic™ 360 automated specimen processing system with the chemagic™ Prime Viral DNA/RNA 300 Kit H96. Complementary DNA synthesis and library preparation was performed using the Illumina COVIDSeq Test kit. Libraries were pooled, quantified, normalized, and sequenced on a NovaSeq™ 6000 Sequencing System.

Sequence files were analyzed using the Illumina DRAGEN COVIDSeq Test App in BaseSpace Sequence Hub. The COVIDSeq Test leveraged 98 amplicons to amplify SARS-CoV-2-specific sequences, and for samples with 90 or more SARS-CoV-2 amplicons detected, the DRAGEN COVIDSeq Test Pipeline generated a consensus sequence in FASTA format and performed variant calling. The Pango Lineage is reported. The COVIDSeq method was performed at Infinity BiologiX in Piscataway, NJ, USA. The COVIDSeq assay workflow for SARS-CoV-2 strain determination was validated for saliva samples as a biospecimen.

Statistical Analysis

Safety analyses were based on the safety analysis set, defined as all participants who received 1 or more dose of trial treatment and grouped based on actual treatment obtained. Adverse events (AE) severity was graded according to a revised US Food and Drug Administration toxicity grading guidance[2] and coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1). Safety data were analyzed descriptively.

All efficacy analyses were based on the fully vaccinated analysis set (FVAS) unless otherwise specified, which included all participants who were SARS-CoV-2 seronegative at baseline, received two doses of trial intervention, and who remained in the trial 15 days or more after their second dose without having had a prior confirmed SARS-CoV-2 RT-PCR–positive infection. A blinded, independent, efficacy adjudication committee reviewed relevant data of potential cases for Covid-19–related efficacy endpoint evaluations. Efficacy analyses included only illnesses independently adjudicated as Covid-19 events.

A Poisson regression model with robust variance[3] adjusted for follow-up time, was used as the primary efficacy analysis model to estimate the relative risk of the incidence of symptomatic infection between the AZD1222 and placebo groups. The model contained the trial group and age group at the time of informed consent (≥18 to <65 years, versus ≥65 years) as covariates. The logarithm of the participant's corresponding monitoring period at risk, starting from 15 days or more after the second dose of trial intervention up to either the event, data cut-off, the date of unmasking or EUA vaccine, date of early withdrawal or the date of a SARS-CoV-2 RT-PCR–positive infection not meeting the endpoint definition, whichever occurred first, was used as an offset variable in the model to adjust for participants having different exposure times during which the events occurred. The null hypothesis used for the primary efficacy endpoint was that vaccine efficacy is equal to 30%.

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. Although non-Covid-19 deaths are a competing risk, given that all deaths were independently adjudicated and there was no imbalance between groups censoring at the date of non-Covid death would not be expected to impact the results.

This analysis was repeated for the secondary endpoints of symptomatic Covid-19 regardless of prior SARS-COV-2 infection, symptomatic Covid-19 according to the CDC criteria, Covid-19 related Emergency Department visits and post-treatment response, as well as the exploratory endpoint of Covid-19-related hospitalizations. For the key secondary endpoint of severe or critical Covid-19, a stratified exact Poisson regression model was used, with age group at the time of informed consent (≥18 to <65 years, or ≥65 years) as the strata. The number of events for each combination of treatment and strata was used as the response variable and the logarithm of total number of participants for each combination of treatments and strata was used as an offset variable in the model. Given that the AZD1222 group had 0 events, the maximum likelihood estimate for the relative risk was zero, corresponding to a vaccine efficacy of 100%, and the 1-sided 97.5% confidence interval was presented. A supportive analysis of the time to primary efficacy endpoint was performed using a Cox proportional hazards model, where the vaccine efficacy was estimated as 1- hazard ratio

(HR), where HR was the ratio of the incidence in the AZD1222 group relative to the incidence in the placebo group expressed as a percentage. In addition, a sensitivity analysis using a multiple imputation approach to evaluate the robustness of the primary analysis of the primary endpoint, the missing outcome for participants with truncated follow-up (eg, trial withdrawal, lost to follow-up, death not caused by SARS-CoV-2, unmasking or EUA vaccination) prior to reaching the data cut-off without a primary endpoint event was imputed by age group stratum using the event rate per treatment group under the assumption of missing at random. The imputation was carried out using SAS PROC MI (Monotone Logistic Regression Method) and was repeated 20 times. SAS PROC MIANALYZE was used to combine inferences from the 20 completed datasets.

For the primary efficacy analysis, approximately 150 events meeting the primary efficacy endpoint definition were required across the AZD1222 and placebo groups within the population of participants who were seronegative at baseline to detect a vaccine efficacy of 60% with >90% power. These calculations assumed an observed attack rate of 0.8% and were based on a two-sided test, where the lower bound of the two-sided multiplicity-adjusted confidence interval (CI) for vaccine efficacy is required to be >30% with an observed point estimate of at least 50%. Sample size calculations accounted for an interim analysis at approximately 75 events (when approximately 50% of the total amount of statistical information is available) and a primary analysis at approximately 150 events, the timing of which were driven by the number of events in the trial, assuming minimal loss to follow-up as it was anticipated that participants would remain engaged in the trial. A Lan-DeMets alpha-spending function was used to account for multiplicity across the interim and primary analyses such that the overall Type I error was controlled at 5%. If exactly 75 cases were analyzed at the interim and 150 cases at the primary analysis, the alpha levels would have been, 0.31% and 4.9%, respectively. Given the interim analysis was actually carried out with 141 cases, in accordance with the pre-planned Lan-DeMets alpha-spending function, the alpha level used for the interim was 4.16%. Given the criteria for evidence of efficacy were met at the interim analysis, the primary analysis was carried out at the nominal 5% alpha level.

The key secondary endpoints were tested at the adjusted significance level using hierarchical fixed-sequence testing in the order below. If the two-sided multiplicity-adjusted CI was >0%, then analysis proceeded to the next endpoint:

1 Key Secondary Endpoint 1: Incidence of the first case of SARS-CoV-2 RT-PCR–positive symptomatic illness occurring 15 days or more after the second dose of trial intervention regardless of evidence of prior SARS-CoV-2 infection
2 Key Secondary Endpoint 2: Incidence of the first case of SARS-CoV-2 RT-PCR–positive severe or critical symptomatic Covid-19 occurring 15 days or more after the second dose of trial intervention
3 Key Secondary Endpoint 3: Incidence of Covid-19-related Emergency Department visits occurring 15 days or more after the second dose of trial intervention.
4 Key Secondary Endpoint 4: Incidence of the first post-treatment response (negative at baseline to positive post treatment with trial intervention) for SARS-CoV-2 nucleocapsid antibodies occurring 15 days or more after the second dose of trial intervention

A primary efficacy analysis was planned to be conducted when approximately 150 events meeting the primary efficacy endpoint definition had been reported across the AZD1222 and placebo groups within the population of participants who were seronegative for SARS-CoV-2 at baseline. The interim analysis data package (with the data cut-off date of February 17, 2021) was delivered by the independent statistical group to the Data Safety Monitoring Board (DSMB) on March 11, 2021. Following independent review and additional analyses, on March 17, 2021, the DSMB determined that the interim analysis criteria had been met for the primary efficacy endpoint and the trial team could move forward with the full interim analysis. A decision was therefore made to proceed with unblinding of the trial results as of March 18, 2021. Based on data accumulated up to March 17, 2021, there were >150 adjudicated primary endpoint events in the FVAS. Given >150 adjudicated primary endpoint events had been reached at this time, the primary analysis was conducted. A data cut-off date of March 5, 2021, corresponding to the start date of the last adjudicated event meeting the primary endpoint definition, was therefore applied to the unblinded data transfer, received on March 19, 2021. An initial primary analysis was conducted in parallel to the adjudication of 14 outstanding potential cases. Following confirmation that all events prior to the data cut-off

had been fully adjudicated, the data analysis was refreshed and updated to ensure that all cases were appropriately included in the data set being reported.

Subgroup analyses were performed on the following groups where sufficient cases were observed:

- Age group at informed consent (≥18 to <65 years and ≥65 years)
- Sex
- 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
- Ethnicity
- Country of enrollment
- Covid-19 coexisting conditions at baseline

A further secondary endpoint of the incidence of the first case of SARS-CoV-2 RT-PCR–positive symptomatic illness occurring 15 days or more after the second dose of trial intervention using CDC criteria[4] was analyzed using the symptoms presented as "qualifying symptoms" above. For this endpoint, participants were only required to have qualifying symptoms for 1 or more days.

SUPPLEMENTARY RESULTS

Clinical Hold

On September 9, 2020, the trial was placed on clinical hold due to an event of transverse myelitis reported in a different AZD1222 clinical trial.[5] After a review of the event and all available safety data, the US Food and Drug Administration deemed it was safe to lift the clinical hold on October 23, 2020 and the trial resumed on October 28, 2020. Enhanced safety monitoring and reporting procedures were implemented for the AZD1222 trials. As a consequence of this hold ~800 participants had a dosing interval >4 weeks and are included in the safety analysis set as randomized and are included in the FVAS where meeting the criteria for inclusion.

A total of 775 participants (2.4%) in the safety analysis set were impacted by the clinical hold and received their second dose outside of the planned 28-day window.

Unmasking

Due to the availability of other Covid-19 vaccines under EUA, trial participants eligible for receipt of a vaccine were unmasked beginning December 14, 2020. Overall, data from 6100 (34.5%) participants in the FVAS fully vaccinated analysis set were censored at the time of unmasking in the AZD1222 group, and 3253 (38.0%) in the placebo group.

Efficacy

Due to the urgency of data dissemination required during the pandemic setting, the initial estimated vaccine efficacy using the primary dataset, which did not include 14 potential cases that were pending adjudication, was publicly disclosed (76.0%, 95% CI 67.6–82.2, P<0.001). Once adjudication of all events before the data cut-off (March 5, 2021) was complete, 203 symptomatic Covid-19 events met the case definition of the primary endpoint and were included in the updated primary analysis for the fully vaccinated analysis set (AZD1222 n=17,662, placebo n=8550) (**Figure 1)**. All following presented analyses are based on the updated primary analysis of the censored group.

The estimated vaccine efficacy for incidence of first SARS-CoV-2 RT-PCR–positive symptomatic illness occurring post first dose of trial intervention among participants in the full analysis set who were SARS-CoV-2 seronegative at baseline was 54.5% (95% CI 46.5–

61.3) based on 287 cases out of 20,302 (1.4%) in the AZD1222 group and 303 cases out of 9997 (2.9%) in the placebo group. The cumulative incidence of first SARS-CoV-2 RT-PCR–positive symptomatic illness following the first dose of AZD1222 is shown in **Figure S1**.

Estimated vaccine efficacy against infection was 64.3% (95% CI 56.1–71.0, P<0.001), with 156 seroconversions (0.9%) in the AZD1222 and 202 seroconversions (2.4%) in the placebo group. As a result of the 2:1 randomization, the total follow-up time was 2000 person years for AZD1222 and 900 person years for placebo. Incidence rate (cases per 1000 person-years) was 76.9 for AZD1222 and 215.4 for placebo participants.

Further investigations to determine the potential impact of circulating SARS-CoV-2 variants on AZD1222 vaccine efficacy are ongoing.

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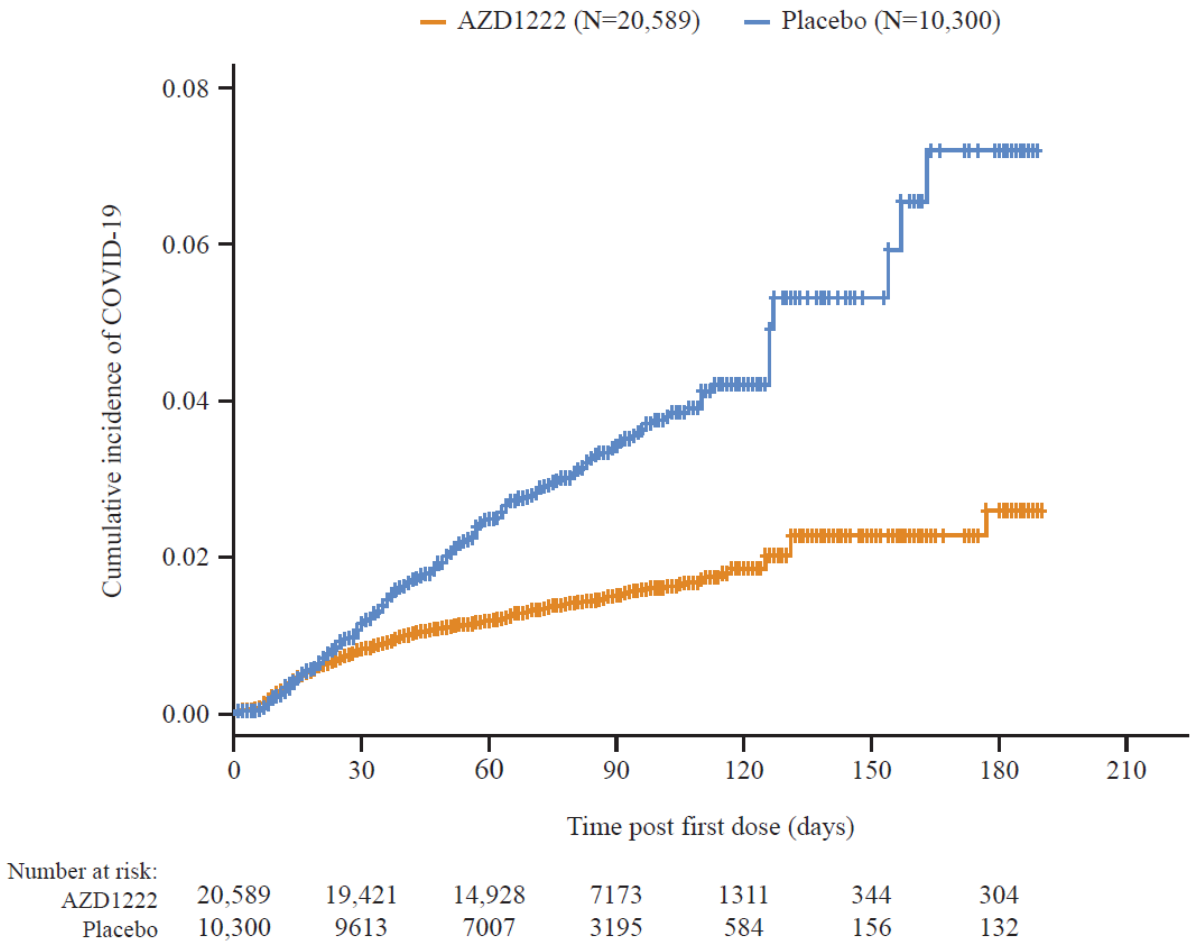
SUPPLEMENTARY FIGURES

Figure S1. Time to First SARS-CoV-2 RT-PCR–Positive Symptomatic Illness Occurring after the First Dose, (Full Analysis Set, Seronegative at Baseline).

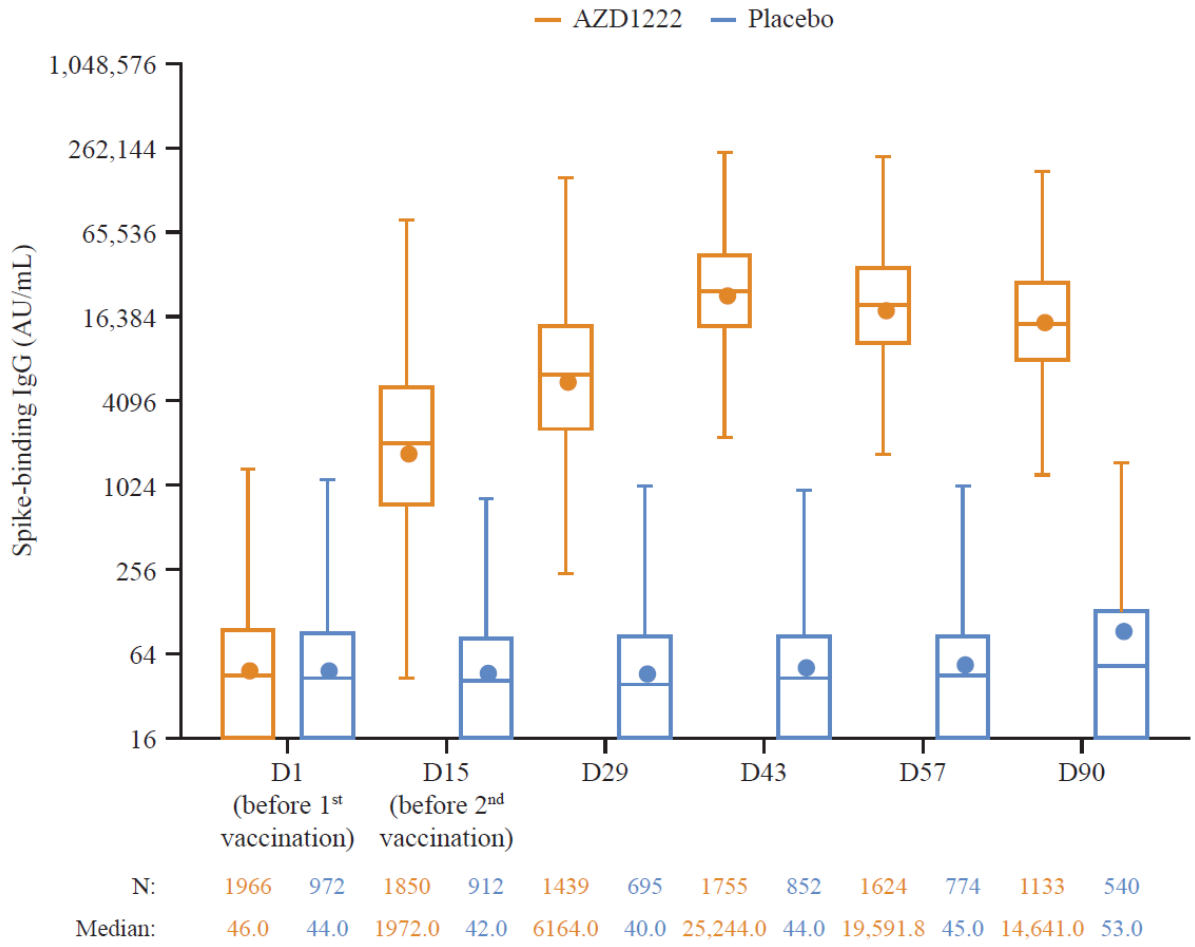


The time to event was calculated as: (date of first SARS-CoV-2 RT-PCR–positive test occurring post first dose) – (date of first dose of trial intervention) + 1. For censored participants, the censoring time was from date of first dose of trial intervention to last time observed prior to data cut-off (March 5, 2021). Cumulative incidence of Covid-19 estimated using Kaplan-Meier method.

Tick marks indicate censored data.

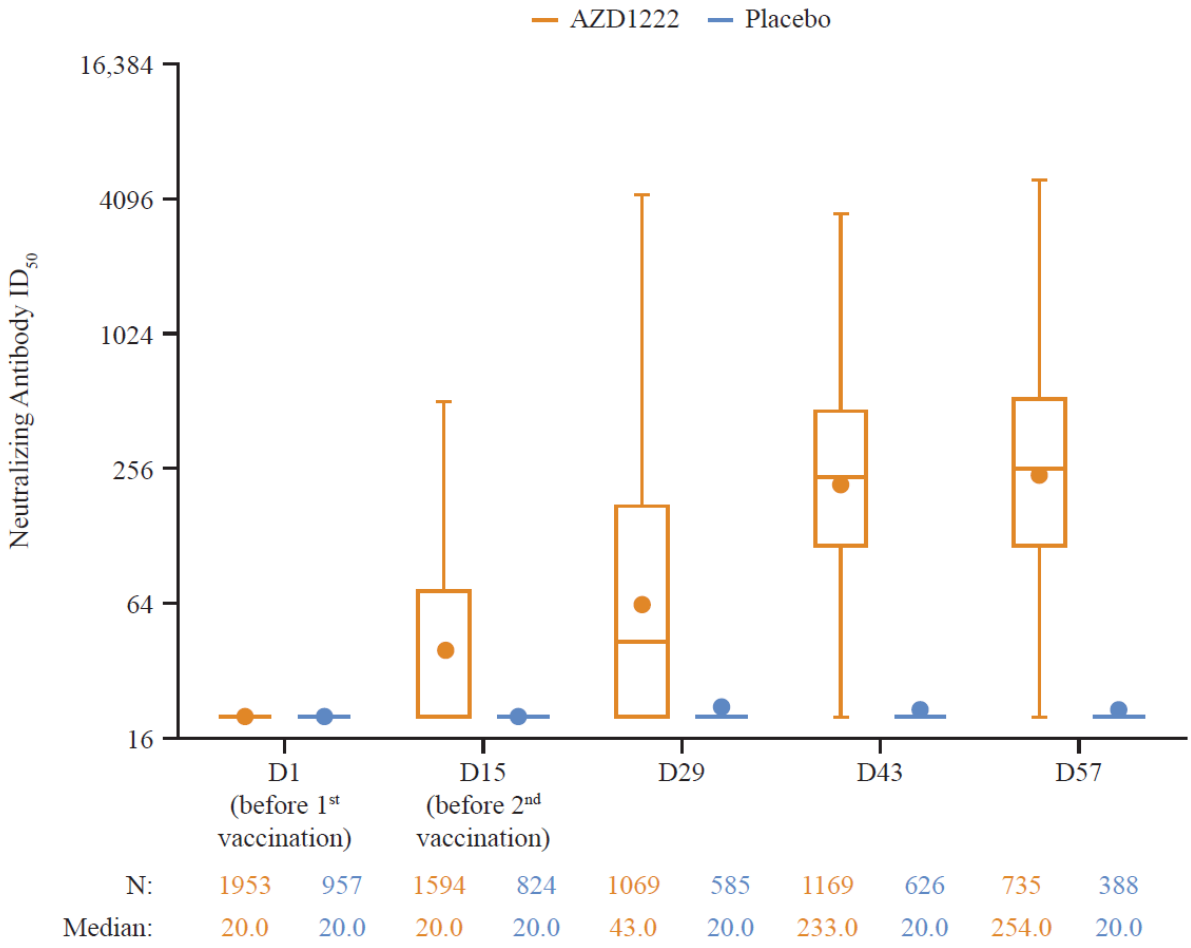
Covid-19, coronavirus disease 2019; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure S2. Quantitation of SARS-Cov-2 Spike IgG Over Time (Substudy Analysis Set)



The box denotes IQR, the line inside the box denotes median, the marker inside the box is the geometric mean. Any points >1.5×IQR from the box were considered outliers and are not displayed. The whiskers that extend from the box indicate the minimum and maximum after removing the outliers. Boxplots are created using the log-normal distribution. D1 is the last non-missing value taken prior to the first dose. Titer values measured as <LLoQ (33 AU/mL) were imputed to a value that is half of the LLoQ. Titer values measured as >ULoQ (2,000,000 AU/mL) were imputed at the ULoQ value.
AU, arbitrary units; D, day; IgG, immunoglobulin G; IQR, interquartile range; LLoQ, lower limit of quantification; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULoQ, upper limit of quantification.

Figure S3. Quantitation of SARS-Cov-2 Neutralizing Antibody Over Time (Substudy Analysis Set)



The box denotes IQR, the line inside the box denotes median, the marker inside the box is the geometric mean. Any points >1.5×IQR from the box were 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. D1 is the last non-missing value taken prior to the first dose. Titer values measured as <LLoQ (40 ID_{50}) were imputed to a value that is half of the LLoQ. Titer values measured as >ULoQ (787,339 ID_{50}) were imputed at the ULoQ value.

D, day; ID_{50}, inhibitory dilution (50%) IQR, interquartile range; LLoQ, lower limit of quantification; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULoQ, upper limit of quantification.

SUPPLEMENTARY TABLES

Table S1. Demographic and Clinical Characteristics of the Fully Vaccinated Analysis Set at Baseline*

Characteristic	AZD1222 (N=17,662)	Placebo (N=8550)	Total (N=26,212)
Age – yr†			
Mean	49.8±15.7	49.9±15.7	49.9±15.7
Median	51.0	51.0	51.0
Range	18–99	18–91	18–99
Age group – no. (%)			
≥18 to 64 yr	13,966 (79.1)	6738 (78.8)	20,704 (79.0)
≥65 yr	3696 (20.9)	1812 (21.2)	5508 (21.0)
Sex – no. (%)			
Male	9922 (56.2)	4829 (56.5)	14,751 (56.3)
Female	7740 (43.8)	3721 (43.5)	11,461 (43.7)
Hispanic or Latinx ethnic group– no. (%)‡			
No	13,351 (75.6)	6370 (74.5)	19,721 (75.2)
Yes	4035 (22.8)	2064 (24.1)	6099 (23.3)
Not reported	238 (1.3)	106 (1.2)	344 (1.3)
Unknown	38 (0.2)	10 (0.1)	48 (0.2)
Race or ethnic group – no. (%)‡			
White	14,011 (79.3)	6755 (79.0)	20,766 (79.2)
Black or African American	1401 (7.9)	706 (8.3)	2107 (8.0)
Asian	747 (4.2)	352 (4.1)	1099 (4.2)
American Indian or Alaska Native	744 (4.2)	373 (4.4)	1117 (4.3)
Multiple	421 (2.4)	202 (2.4)	623 (2.4)
Native Hawaiian or other Pacific Islander	50 (0.3)	14 (0.2)	64 (0.2)
Not reported	207 (1.2)	110 (1.3)	317 (1.2)
Unknown	81 (0.5)	38 (0.4)	119 (0.5)
Country – no. (%)			
United States	15,435 (87.4)	7443 (87.1)	22,878 (87.3)
Chile	1360 (7.7)	672 (7.9)	2032 (7.8)
Peru	867 (4.9)	435 (5.1)	1302 (5.0)
Coexisting conditions – no. (%)§			
Any coexisting condition at baseline	10,376/17,661 (58.8)	5105/8549 (59.7)	15,481/26,210 (59.1)
History of obesity‖	4735/17,661 (26.8)	2387/8549 (27.9)	7122/26,210 (27.2)
High blood pressure	4712/17,661 (26.7)	2262/8549 (26.5)	6974/26,210 (26.6)
History of smoking	3359/17,661 (19.0)	1655/8549 (19.4)	5014/26,210 (19.1)
Asthma	1727/17,661 (9.8)	890/8549 (10.4)	2617/26,210 (10.0)
Type 2 diabetes	1228/17,661 (7.0)	662/8549 (7.7)	1890/26,210 (7.2)

Serious heart conditions	567/17,661 (3.2)	258/8549 (3.0)	825/26,210 (3.1)
Liver disease	268/17,661 (1.5)	132/8549 (1.5)	400/26,210 (1.5)
COPD	238/17,661 (1.3)	142/8548 (1.7)	380/26,209 (1.4)
Cerebrovascular diseases	173/17,661 (1.0)	85/8549 (1.0)	258/26,210 (1.0)
Chronic kidney disease	129/17,661 (0.7)	43/8549 (0.5)	172/26,210 (0.7)
Type 1 diabetes	100/17,661 (0.6)	60/8549 (0.7)	160/26,210 (0.6)
Thalassemia	29/17,661 (0.2)	17/8549 (0.2)	46/26,210 (0.2)
Scarring in the lungs: pulmonary fibrosis	28/17,661 (0.2)	10/8549 (0.1)	38/26,210 (0.1)
Dementia	6/17,661 (<0.1)	7/8549 (<0.1)	13/26,210 (<0.1)
Sickle cell disease	5/17,661 (<0.1)	5/8549 (<0.1)	10/26,210 (<0.1)
Lower immune health due to solid organ transplantation	5/17,660 (<0.1)	2/8549 (<0.1)	7/26,209 (<0.1)
Cystic fibrosis	0/17,661	0/8549	0/26,210

[*]Plus-minus values are mean ±SD. Data shown are from the fully vaccinated analysis population. Numbers are based on trial intervention actually received. COPD denotes chronic obstructive pulmonary disease.

[†]Age reflects the age at the date of signed informed consent.

[‡]Race and ethnic group were reported by the participant. The same questions and categories used to determine participant race and ethnic group were used for all countries and sites. American Indian includes participants who indicated they were South American and participants who were indigenous to Peru. Multiple includes participants who reported that they were of more than one race.

[§]Percentages for coexisting conditions were calculated on the basis of participants with available data.

[‖]Obesity is a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) greater than 30.

Table S2. Overall Summary of Unsolicited AEs Reported Within 28 Days of Any Dose for the Safety Analysis Set

	AZD1222 (N=21,587)		Placebo (N=10,792)	
	No. patients (%)	**No. events**	**No. patients (%)**	**No. events**
Any AE	8771 (40.6)	17,491	3201 (29.7)	6047
Any AE related to trial intervention	6238 (28.9)	10,912	1525 (14.1)	2563
Related AE – Mild	4994 (23.1)	9287	1291 (12.0)	2266
Related AE – Moderate	1198 (5.5)	1574	220 (2.0)	283
Related AE – Severe	46 (0.2)	51	14 (0.1)	14
Any AE Grade 3 or higher	225 (1.0)	267	116 (1.1)	138
Any non-serious AE	8731 (40.4)	17,372	3180 (29.5)	5984
Any SAE	101 (0.5)	119	53 (0.5)	59
Any SAE related to trial intervention	1 (<0.1)	1	1 (<0.1)	1
Any AE with outcome of death, entire trial*	7 (<0.1)	7	7 (<0.1)	9
Related AEs with outcome of death	0	0	0	0
AEs leading to discontinuation from trial intervention	266 (1.2)	276	162 (1.5)	163
Related AEs leading to trial discontinuation	22 (0.1)	31	7 (<0.1)	7
Any AE leading to discontinuation from trial	3 (<0.1)	3	5 (<0.1)	5
Any MAAE	1288 (6.0)	1649	632 (5.9)	830
Any AESI	442 (2.0)	469	319 (3.0)	346
Any AESI related to trial intervention	58 (0.3)	66	26 (0.2)	34

Multiple events in the same category are counted only once for that category for number of participants. Events in 1 or more category are counted once in each applicable category.
Includes AEs with an onset date on or after the day of first dose for the applicable reporting period. Data presented are pooled values for AEs reported within 28 days of any dose. SAEs, MAAEs and AESIs are reported through trial completion or withdrawal.
*No. deaths (%), no. events that led to the outcome of death during the entire trial. One patient may have experienced more than one event that led to death. AEs with an outcome of death in the AZD1222 group were overdose (n=2), death (unspecified) (n=1), toxic shock syndrome (n=1), accident (n=1), road traffic accident (n=1), and toxicity to various agents (n=1). AEs with an outcome of death in the placebo group were Covid-19 pneumonia (n=2), cardiac arrest (n=1), death (unspecified) (n=1), septic shock (n=1), diabetic ketoacidosis (n=1), hemorrhagic transformation stroke (n=1), ischemic stroke (n=1), and asphyxia (n=1).
AE, adverse event; AESI, AE of special interest; Covid-19, coronavirus disease 2019; MAAE, medically-attended AE; SAE, serious AE; SD, standard deviation.

Table S3. Related Unsolicited SAEs by System Organ Class and Preferred Term for the Safety Analysis Set

	AZD1222 (N=21,587)		Placebo (N=10,792)	
	No. patients (%)	**No. events**	**No. patients (%)**	**No. events**
Participants with 1 or more related SAE	1 (<0.1)	2	2 (<0.1)	2
Ear and labyrinth disorders	0	0	1 (<0.1)	1
Neurosensory hypoacusis	0	0	1 (<0.1)	1
Eye disorders	0	0	1 (<0.1)	1
Optic ischemic neuropathy	0	0	1 (<0.1)	1
Nervous system disorders	1 (<0.1)	2	0	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (<0.1)	1	0	0
Hypoesthesia	1 (<0.1)	1	0	0

SAE, serious adverse event.

Table S4. Related Unsolicited MAAEs by System Organ Class and Preferred Term for the Safety Analysis Set

	AZD1222 (N=21,587)		Placebo (N=10,792)	
	No. patients (%)	**No. events**	**No. patients (%)**	**No. events**
Participants with 1 or more related MAAE	78 (0.4)	112	27 (0.3)	40
Cardiac disorders	2 (<0.1)	2	0	0
Palpitations	1 (<0.1)	1	0	0
Tachycardia	1 (<0.1)	1	0	0
Ear and labyrinth disorders	3 (<0.1)	3	3 (<0.1)	3
Tinnitus	2 (<0.1)	2	0	0
Vertigo	1 (<0.1)	1	1 (<0.1)	1
Neurosensory hypoacusis	0	0	1 (<0.1)	1
Sudden hearing loss	0	0	1 (<0.1)	1
Eye disorders	0	0	2 (<0.1)	2
Eye swelling	0	0	1 (<0.1)	1
Optic ischemic neuropathy	0	0	1 (<0.1)	1
Gastrointestinal disorders	6 (<0.1)	8	3 (<0.1)	3
Diarrhea	3 (<0.1)	3	0	0
Paresthesia oral	1 (<0.1)	1	1 (<0.1)	1
Abdominal pain upper	0	0	1 (<0.1)	1
Bowel movement irregularity	1 (<0.1)	1	0	0
Gastroesophageal reflux disease	1 (<0.1)	1	0	0
Lip swelling	1 (<0.1)	1	0	0
Parotid gland enlargement	0	0	1 (<0.1)	1
Vomiting	1 (<0.1)	1	0	0
General disorders and administration site conditions	20 (<0.1)	22	5 (<0.1)	5
Pain	6 (<0.1)	6	0	0
Fatigue	3 (<0.1)	3	1 (<0.1)	1
Influenza-like illness	2 (<0.1)	2	0	0
Asthenia	1 (<0.1)	1	0	0
Chest pain	0	0	1 (<0.1)	1
Chills	0	0	1 (<0.1)	1
Discomfort	1 (<0.1)	1	0	0
Feeling hot	1 (<0.1)	1	0	0
Injection site erythema	1 (<0.1)	1	0	0
Injection site pain	1 (<0.1)	1	0	0
Injection site paresthesia	1 (<0.1)	1	0	0
Injection site pruritus	1 (<0.1)	1	0	0
Injection site reaction	1 (<0.1)	1	0	0
Injury associated with device	0	0	1 (<0.1)	1
Non-cardiac chest pain	1 (<0.1)	1	0	0
Peripheral swelling	1 (<0.1)	1	0	0
Reactogenicity event	0	0	1 (<0.1)	1
Swelling	1 (<0.1)	1	0	0
Immune system disorders	2 (<0.1)	2	0	0
Drug hypersensitivity	1 (<0.1)	1	0	0

Hypersensitivity	1 (<0.1)	1	0	0
Infections and infestations	6 (<0.1)	6	1 (<0.1)	1
Herpes zoster	4 (<0.1)	4	0	0
Cellulitis	1 (<0.1)	1	0	0
Injection site cellulitis	1 (<0.1)	1	0	0
Nasopharyngitis	0	0	1 (<0.1)	1
Injury, poisoning, and procedural complications	3 (<0.1)	3	2 (<0.1)	2
Injection-related reaction	0	0	2 (<0.1)	2
Chilblains	1 (<0.1)	1	0	0
Seroma	1 (<0.1)	1	0	0
Skin laceration	1 (<0.1)	1	0	0
Investigations	3 (<0.1)	3	0	0
Body temperature increased	3 (<0.1)	3	0	0
Metabolism and nutrition disorders	3 (<0.1)	4	0	0
Dehydration	1 (<0.1)	1	0	0
Hyperlactacidemia	1 (<0.1)	1	0	0
Hypokalemia	1 (<0.1)	1	0	0
Vitamin B12 deficiency	1 (<0.1)	1	0	0
Musculoskeletal and connective tissue disorders	9 (<0.1)	9	5 (<0.1)	5
Arthralgia	3 (<0.1)	3	0	0
Back pain	0	0	2 (<0.1)	2
Muscle fatigue	0	0	1 (<0.1)	1
Muscle spasms	1 (<0.1)	1	0	0
Muscular weakness	1 (<0.1)	1	0	0
Musculoskeletal pain	1 (<0.1)	1	0	0
Myalgia	0	0	1 (<0.1)	1
Neck pain	1 (<0.1)	1	0	0
Pain in jaw	0	0	1 (<0.1)	1
Polymyalgia rheumatica	1 (<0.1)	1	0	0
Rheumatoid arthritis	1 (<0.1)	1	0	0
Nervous system disorders	23 (0.1)	29	3 (<0.1)	8
Paresthesia	8 (<0.1)	8	2 (<0.1)	5
Hypoesthesia	4 (<0.1)	4	1 (<0.1)	2
Dizziness	3 (<0.1)	4	1 (<0.1)	1
Headache	4 (<0.1)	4	0	0
Syncope	2 (<0.1)	2	0	0
Ageusia	1 (<0.1)	1	0	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (<0.1)	1	0	0
Facial paralysis	1 (<0.1)	1	0	0
Guillain-Barré syndrome	1 (<0.1)	1	0	0
Migraine	1 (<0.1)	1	0	0
Occipital neuralgia	1 (<0.1)	1	0	0
Tremor	1 (<0.1)	1	0	0
Psychiatric disorders	2 (<0.1)	3	0	0
Anxiety	1 (<0.1)	1	0	0
Depression	1 (<0.1)	1	0	0
Insomnia	1 (<0.1)	1	0	0

Respiratory, thoracic, and mediastinal disorders	8 (<0.1)	9	4 (<0.1)	6
Nasal congestion	3 (<0.1)	3	1 (<0.1)	1
Cough	2 (<0.1)	2	1 (<0.1)	1
Dyspnea	2 (<0.1)	2	1 (<0.1)	1
Oropharyngeal pain	1 (<0.1)	1	2 (<0.1)	2
Sinus congestion	1 (<0.1)	1	0	0
Sneezing	0	0	1 (<0.1)	1
Skin and subcutaneous tissue disorders	6 (<0.1)	7	5 (<0.1)	5
Dermatitis allergic	1 (<0.1)	1	1 (<0.1)	1
Rash maculo-papular	1 (<0.1)	1	1 (<0.1)	1
Urticaria	2 (<0.1)	2	0	0
Dermatitis	0	0	1 (<0.1)	1
Neurodermatitis	0	0	1 (<0.1)	1
Petechiae	0	0	1 (<0.1)	1
Pruritus	1 (<0.1)	2	0	0
Seborrheic dermatitis	1 (<0.1)	1	0	0
Vascular disorders	2 (<0.1)	2	0	0
Hypertension	2 (<0.1)	2	0	0

MAAEs are AEs leading to medically-attended visits that were not routine visits for physical examination, vaccination, or illness visit, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine trial visit or during the scheduled illness visits were not be considered. MAAEs are reported through trial completion or withdrawal.
AE, adverse event; MAAE, medically attended adverse event.

Table S5. Related Unsolicited AESIs by Category and Preferred Term for the Safety Analysis Set

	AZD1222 (N=21,587)		Placebo (N=10,792)	
	No. patients (%)	**No. events**	**No. patients (%)**	**No. events**
Participants with 1 or more related AESI	58 (0.3)	68	26 (0.2)	34
Participants with any neurologic and/or neuroinflammatory related AESI	56 (0.3)	66	26 (0.2)	34
Neurologic[*]	55 (0.3)	65	26 (0.2)	34
Paresthesia	34 (0.2)	37	16 (0.1)	22
Hypoesthesia	14 (<0.1)	15	4 (<0.1)	5
Muscular weakness	7 (<0.1)	7	1 (<0.1)	1
Dysesthesia	0	0	3 (<0.1)	3
Hyperesthesia	3 (<0.1)	3	0	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (<0.1)	1	0	0
Guillain-Barré syndrome	1 (<0.1)	1	0	0
Neuritis	0	0	1 (<0.1)	1
Neuropathy peripheral	1 (<0.1)	1	0	0
Polyneuropathy	0	0	1 (<0.1)	1
Sensory disturbance	0	0	1 (<0.1)	1
Potential Immune-Mediated Conditions	4 (<0.1)	5	1 (<0.1)	1
Musculoskeletal disorders	2 (<0.1)	2	0	0
Polymyalgia rheumatica	1 (<0.1)	1	0	0
Rheumatoid arthritis	1 (<0.1)	1	0	0
Neuroinflammatory disorders[*]	2 (<0.1)	3	1 (<0.1)	1
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (<0.1)	1	0	0
Facial paralysis	1 (<0.1)	1	0	0
Guillain-Barré syndrome	1 (<0.1)	1	0	0
Polyneuropathy	0	0	1 (<0.1)	1

[*]The preferred terms in this category are included in the neurologic and potential immune-mediated conditions category of neuroinflammatory events.
AESI, adverse event of special interest.

Table S6. Summary of SARS-CoV-2 Variants by Lineage, Based on Whole Genome NGS of Saliva Samples for the Full Analysis Set, Seronegative at Baseline

	AZD1222 (N=20,589)		Placebo (N=10,300)		Total (N=30,889)	
	No. (%)	**IR***	**No. (%)**	**IR**	**No. (%)**	**IR**
Total adjudicated cases	287 (1.39)	64.98	303 (2.94)	142.69	590 (1.91)	90.21
No lineage result†	51 (0.25)	11.55	49 (0.48)	23.08	100 (0.32)	15.29
Not sequenced‡	111 (0.54)	25.13	120 (1.17)	56.51	231 (0.75)	35.32
Total variants sequenced	125 (0.61)	28.30	134 (1.30)	63.10	259 (0.84)	39.60
Variants of concern§						
Delta (B.1.617.2)	0	0	0	0	0	0
Gamma (B.1.1.28.1/P.1)	0	0	0	0	0	0
Alpha (B.1.1.7)	1 (<0.01)	0.23	1 (0.01)	0.47	2 (0.01)	0.31
Beta (B.1.351)	1 (<0.01)	0.23	0	0	1 (<0.01)	0.15
Variants of interest§						
Zeta (B.1.1.28.2/P.2)	0	0	0	0	0	0
Epsilon (B.1.427)	1 (<0.01)	0.23	2 (0.02)	0.94	3 (0.01)	0.46
Epsilon (B.1.429)	7 (0.03)	1.58	7 (0.07)	3.30	14 (0.05)	2.14
Eta (B.1.525)	0	0	0	0	0	0
Iota (B.1.526)	1 (<0.01)	0.23	0	0	1 (<0.01)	0.15
Others						
A	0	0	2 (0.02)	0.94	2 (0.01)	0.31
B	1 (<0.01)	0.23	1 (0.01)	0.47	2 (0.01)	0.31
B.1	14 (0.07)	3.17	17 (0.17)	8.01	31 (0.10)	4.74
B.1.1.1	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.1.220	1 (<0.01)	0.23	1 (0.01)	0.47	2 (0.01)	0.31
B.1.1.222	1 (<0.01)	0.23	5 (0.05)	2.35	6 (0.02)	0.92

B.1.1.231	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.1.29	0	0	2 (0.02)	0.94	2 (0.01)	0.31
B.1.1.291	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.1.296	1 (<0.01)	0.23	1 (0.01)	0.47	2 (0.01)	0.31
B.1.1.304	2 (0.01)	0.45	2 (0.02)	0.94	4 (0.01)	0.61
B.1.1.85	0	0	2 (0.02)	0.94	2 (0.01)	0.31
B.1.110.3	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.111	1 (<0.01)	0.23	0	0	1 (<0.01)	0.15
B.1.139	2 (0.01)	0.45	1 (0.01)	0.47	3 (0.01)	0.46
B.1.181	1 (<0.01)	0.23	0	0	1 (<0.01)	0.15
B.1.2	70 (0.34)	15.85	64 (0.62)	30.14	134 (0.43)	20.49
B.1.216	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.234	4 (0.02)	0.91	7 (0.07)	3.30	11 (0.04)	1.68
B.1.239	2 (0.01)	0.45	0	0	2 (0.01)	0.31
B.1.240	1 (<0.01)	0.23	2 (0.02)	0.94	3 (0.01)	0.46
B.1.241	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.243	5 (0.02)	1.13	4 (0.04)	1.88	9 (0.03)	1.38
B.1.260	1 (<0.01)	0.23	0	0	1 (<0.01)	0.15
B.1.311	1 (<0.01)	0.23	2 (0.02)	0.94	3 (0.01)	0.46
B.1.349	0	0	1 (0.01)	0.47	1 (<0.01)	0.15
B.1.361	3 (0.01)	0.68	1 (0.01)	0.47	4 (0.01)	0.61
B.1.369	2 (0.01)	0.45	1 (0.01)	0.47	3 (0.01)	0.46
B.1.404	1 (<0.01)	0.23	1 (0.01)	0.47	2 (0.01)	0.31
R.1	0	0	1 (0.01)	0.47	1 (<0.01)	0.15

*IR is provided as cases per 1000 person-years (number of cases/follow-up time in years).

†Insufficient sequence coverage for lineage designation.

‡Participants who were not sequenced for a saliva sample (specimen not available, or Ct greater than 30).

§Compiled based upon data from the WHO, MHRA. Described using WHO nomenclature (Pango lineage) where appropriate.

Ct, cycle threshold; IR, incidence rate; MHRA, Medicines and Healthcare products Regulatory Agency; NGS, next-generation sequencing; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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