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.

A Quick Take is 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%).

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.

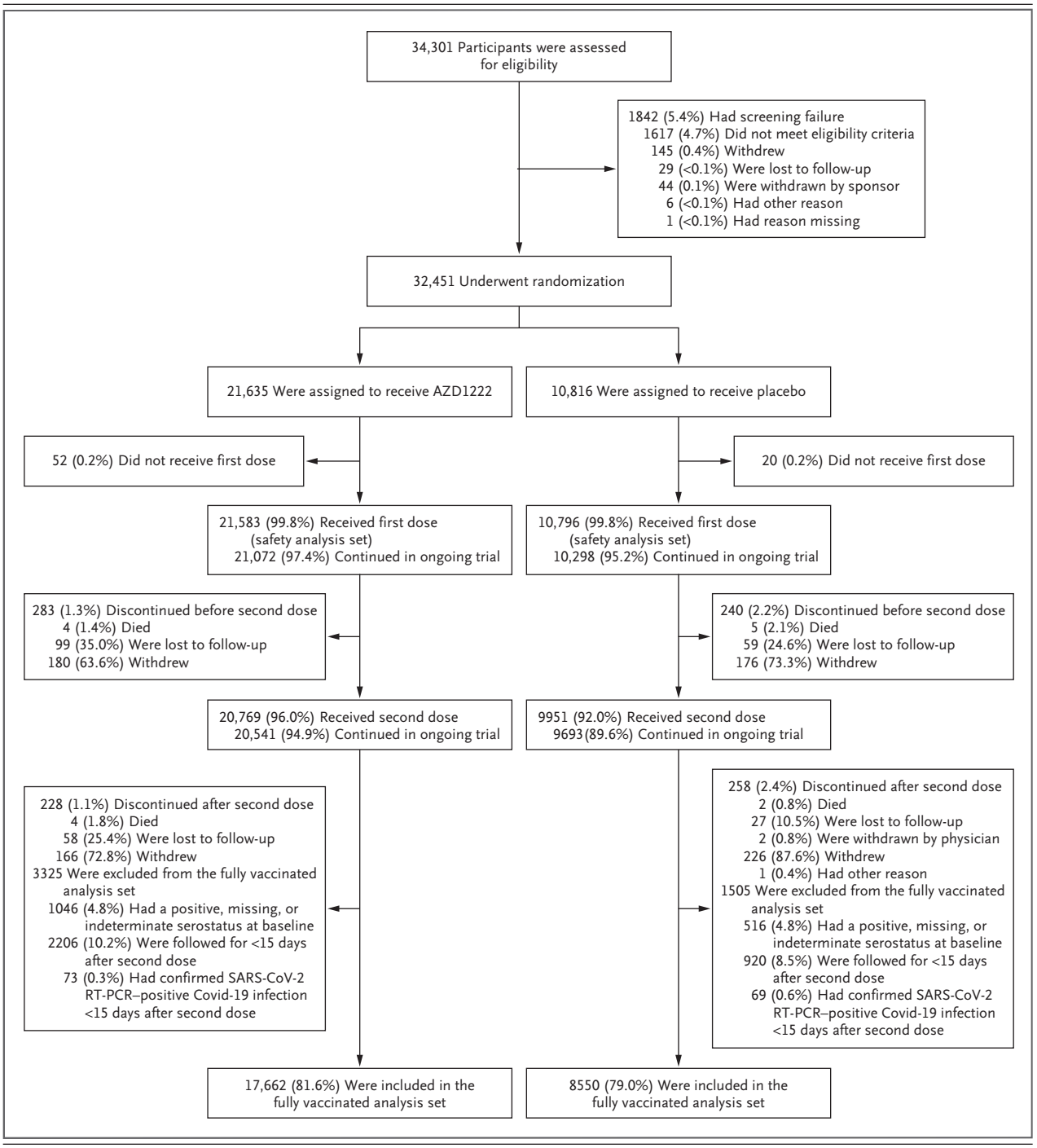
Medically attended adverse events and adverse events of special interest within 28 days after a dose also occurred in similar proportions in the two groups (Table S2). The incidences of individual adverse events related to the vaccine or placebo during the entire trial period are shown in Tables S3 through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

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.

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 infec-

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)
High blood pressure	5851/21,585 (27.1)	2890/10,790 (26.8)	8741/32,375 (27.0)

Table 1. (Continued.)

Characteristic	AZD1222 (N=21,587)	Placebo (N=10,792)	Total (N=32,379)
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.

tion 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

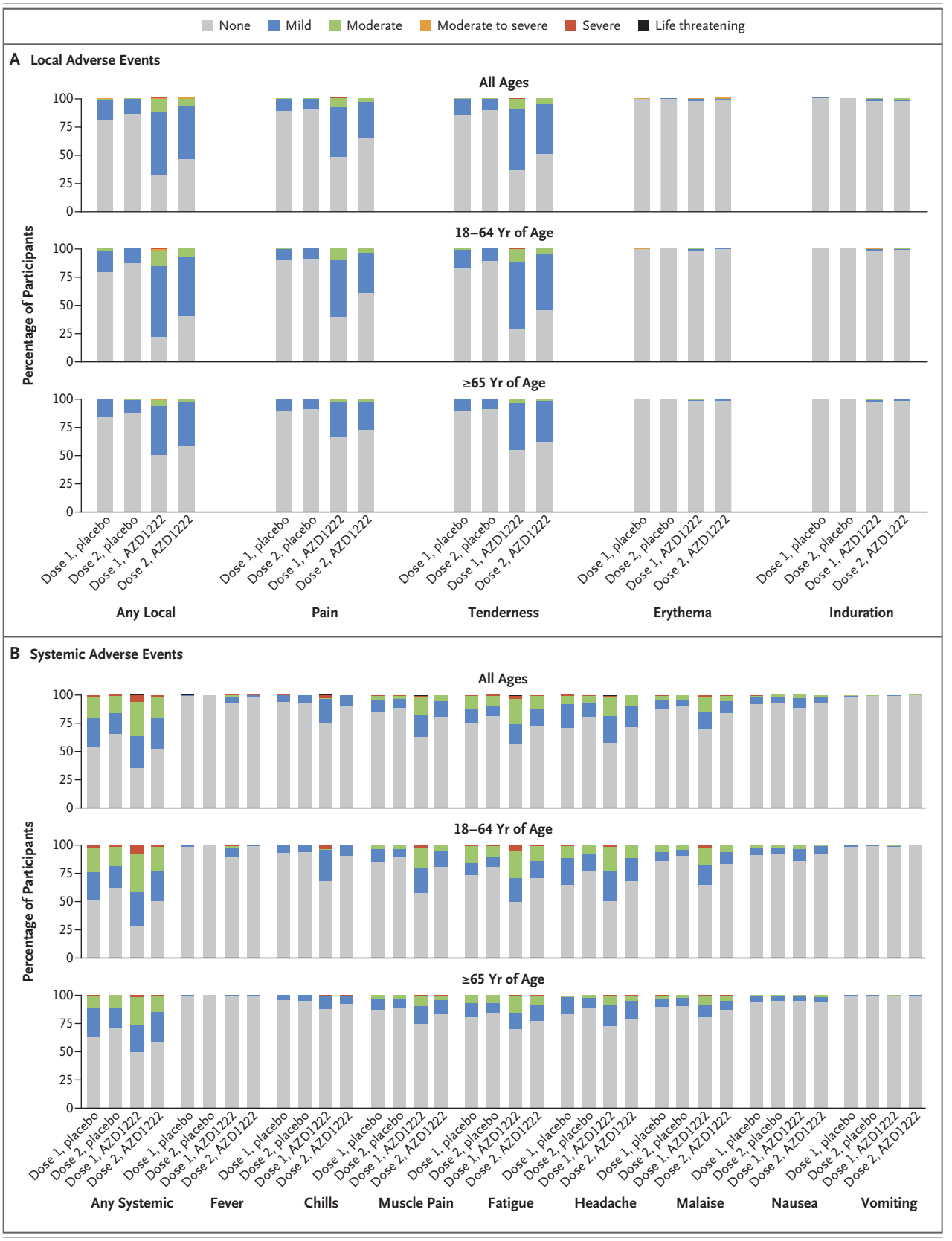


Figure 2 (facing page). Local and Systemic Solicited Adverse Events after First and Second Dose, by Age Group.

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.

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, 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]

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

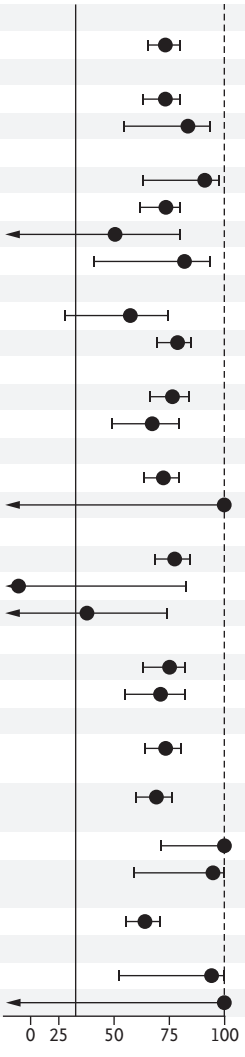


Figure 3. Estimated Vaccine Efficacy ≥15 Days after the Second Dose (Fully Vaccinated Analysis Population).

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 the 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.

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.

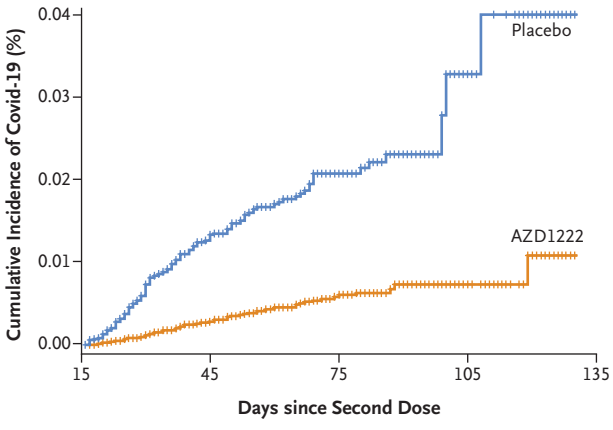


Figure 4. Time to First SARS-CoV-2 RT-PCR–Positive Symptomatic Illness Occurring 15 Days or More after the Second Dose (Fully Vaccinated Analysis Population).

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.

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APPENDIX

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