Supplementary Appendix

Supplement to: Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab–cilgavimab) for prevention of Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2116620

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

Table of contents

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Supplementary methods

Description of the adjudication committee

The adjudication committee was an independent and external committee convened to provide a systematic blinded assessment of whether any deaths during the study were associated with coronavirus disease 2019 (Covid-19). A Charter was developed to document the Committee members' roles, responsibilities, and decision pathways.

The adjudication committee was composed of three members: one Chairperson and two additional physicians, all with expertise in infectious diseases, pulmonary disease, critical care, or virology. The Chairperson was selected based on their expertise in pulmonary critical care.

The Chairperson was responsible for overseeing the operations of the adjudication committee, overseeing meetings, and supervising the flow of data from the committee back to the study sponsor. Committee members were responsible for independently adjudicating deaths occurring in the study according to the clinical trial protocol and adjudication committee Charter.

Adjudication committee members were not study investigators or members of other committees associated with the protocol or study program (e.g., the Data Safety Monitoring Board Committee). Adjudication committee members did not have any serious conflicts of interest that would bias their review of trial data (e.g., financial interests that could be substantially affected by the outcome of the study) and were asked to disclose any conflicts of interest prior to selection. Any conflicts of interest that arose during the study were disclosed at the time of identification. The study

sponsor and Chairperson were notified of any conflicts. Committee members were blinded to participant treatment assignment throughout the adjudication process.

In the event of a study death, two adjudication committee members independently reviewed the complete clinical event packet and rendered their adjudication (Part 1). If the results were concordant, the Chairperson reviewed the event dossier and Part 1 adjudication forms to determine the relatedness of the death to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If this adjudication was concordant, the Chairperson completed the final outcome form, and the adjudication was deemed complete.

If the independent adjudication results from the two adjudication committee members were discordant, the complete clinical event packet was sent to the Chairperson to independently review (Part 2). If this third adjudication was not concordant with either of the first two reviewers, a moderated committee meeting was convened to discuss the relatedness of the death to SARS-CoV-2. Discussion continued until a consensus was reached or members agreed that they were unable to reach final consensus. Requests to the study site to provide additional information could be used to resolve any discordance. If consensus could not be reached through discussion, the Chairperson rendered the final decision.

Study randomization and blinding

Randomization was stratified within each of two cohorts, both capped not to exceed 80% of the total participants randomized. Cohort 1 consisted of adults ≥60 years of age with randomization stratified by long-term care facility residence. Cohort 2 consisted of adults <60 years of age with randomization stratified by risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Participants were centrally assigned to AZD7442 or saline placebo using interactive response technology (IRT). An external third-party vendor (Signant Health; Blue Bell, PA, USA) generated the randomization list using SAS software (SAS Institute, Cary, NC, USA) using random number generation with stratified randomization and random block sizes within each stratum. Before the study was initiated, user guides, log-in information, and directions for the IRT were provided to each study site. AZD7442 was supplied in individual kits of a single-use vial of each of the component monoclonal antibodies (mAbs). Study sites sourced their own saline placebo. An unblinded pharmacist or equivalent at each site prepared and masked dosages and provided syringes to blinded study site staff for administration.

All participants and investigators involved in the dosing, clinical evaluation, and monitoring of the participants were blinded to which randomized drug was received. Blinding could be broken at the investigator's discretion if required, or alternatively at the request of a participant to unblind to determine eligibility for Covid-19 vaccination.

Participant follow-up

For all efficacy endpoints, participants were contacted weekly—by telephone, email, or text message—from baseline with reminders to monitor for Covid-19 symptoms to determine infection incidence. During these weekly contacts, Covid-19 symptoms from the past 7 days were discussed, and illness visits were initiated within 3 days if qualifying symptoms were reported (Table S1). Participants who experienced at least one Covid-19 qualifying symptom were instructed to contact the study site, and participants who presented with a qualifying symptom after day 1 were tested for SARS-CoV-2 at an additional illness visit. Nasopharyngeal swab samples were collected for central SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) testing; if positive, the participant was instructed to continue illness visits up to day 28; if negative, the participant was instructed to stop illness visits and continue with the main scheduled assessments.

Key protocol amendments

The protocol was amended on several occasions as the pandemic evolved. Version 9 (July 26, 2021) was the final version used for analysis. In the original protocol (October 7, 2020), primary analysis of the primary endpoint was scheduled to be conducted when the last dosed participant had been followed through day 183. This was updated to the current analysis from Version 7 (April 7, 2021) onwards. Another amendment (Version 4, December 21, 2020, onwards) allowed participants to unblind if they wished to consider Covid-19 vaccination. A full list of protocol amendments can be found in Version 9 of the protocol which is available online at NEJM.org.

Full inclusion criteria

Participants were eligible for trial inclusion only if all the below criteria were met:

1. Aged ≥18 years at the time of signing the informed consent.
2. Candidate for benefit from passive immunization with antibodies, defined as:
   (a) Increased risk for inadequate response to immunization (predicted poor responder to vaccines):
      - Elderly, i.e., ≥60 years old
      - Obese, i.e., body mass index ≥30 kg/m^2
      - Congestive heart failure
      - Chronic obstructive pulmonary disease
      - Chronic kidney disease, i.e., glomerular filtration rate <30 mL/min/1.73 m^2
      - Chronic liver disease
      - Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines
      - Intolerant of vaccine (defined as previous history of severe adverse event [AE] or serious AE [SAE] after receiving any approved vaccine)
   (b) Increased risk for SARS-CoV-2 infection, defined as individuals whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and Covid-19, based on available risk assessment at time of enrollment. Examples include:
      - Health care workers, including staff of long-term care facilities

- Workers in industrial settings shown to be at high risk for SARS-CoV-2 transmission
- Military personnel residing or working in high-density settings
- Students living in dormitory settings
- Others living in settings of similar close or high-density proximity

3. Medically stable, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the investigator.
4. A negative result from point-of-care SARS-CoV-2 serology testing at screening, using the FaStep Assure tech Point-of-Care (POC)/Fingerstick Fastep® Covid-19 IgG/IgM Rapid Test Device (Assure Tech, Hangzhou, China).
5. Using a predefined method of contraception:
   (a) Male participants must use a condom from day 1 and agree to continue through 365 days following dosing.
   (b) Female participants must either:
      - Not be of childbearing potential (either permanently sterilized [hysterectomy, bilateral oophorectomy, or bilateral salpingectomy] or postmenopausal), or
      - If of childbearing potential, agree to use one highly effective form of contraception (one that can achieve a failure rate of <1% per year when used consistently and correctly) from day 1 and agree to continue through 365 days following dosing, and

- If of childbearing potential, have a negative urine pregnancy test result at visit 1 and throughout the study.

6. Able to understand and comply with study requirements and procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative or equivalent representative as locally defined) based on the assessment of the investigator.
7. Have signed informed consent, if able (participants who were considered by the investigator to be clinically unable to consent at screening and who were entered into the study by the consent of a legally acceptable representative must have shown evidence of assent, as applicable in accordance with local regulations).

Full exclusion criteria

Participants were excluded from the study if any of the below criteria applied:

1. Significant infection or other acute illness, including fever >100°F (>37.8°C) on the day prior to or day of randomization.
2. History of laboratory-confirmed SARS-CoV-2 infection or any positive SARS-CoV-2 result based on available data at screening.
3. History of infection with severe acute respiratory syndrome or Middle East respiratory syndrome.
4. Known history of allergy or reaction to any component of the study drug formulation.
5. Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.

6. Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or Covid-19, or expected receipt during the period of study follow-up.
7. Clinically significant bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular (IM) injections or venipuncture.
8. Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data.
9. Receipt of any investigational medicinal product in the preceding 90 days or expected receipt of investigational medicinal product during the period of study follow-up, or concurrent participation in another interventional study.
10. For women only, currently pregnant (confirmed with positive pregnancy test) or breastfeeding.
11. Blood drawn >450 mL (1 unit) for any reason within 30 days prior to randomization.
12. Employees of the sponsor involved in planning, executing, supervising, or reviewing the AZD7442 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
13. In nations, states, or other jurisdictions that for legal or ethical reasons bar the enrollment of participants who lack capacity to provide their own informed consent, such participants were excluded.

Exclusion criterion 8 was written to allow investigators to use their own judgment about whether a participant should be included in the study for any condition that was not specified in the inclusion and exclusion criteria. Examples might be very sick individuals (e.g., end of life) who would not benefit from participating in the study, or participants with such psychological issues that, based on investigator judgment, would mean they would not be able to comply with study requirements.

Analyses and endpoints

The two key supportive analyses of the primary efficacy endpoint were the first case of SARS-CoV-2 RT-PCR–positive symptomatic illness (regardless of unblinding or receipt of a Covid-19 vaccine), and the first case of SARS-CoV-2 RT-PCR–positive symptomatic illness including all deaths.

The key secondary efficacy endpoint was the incidence of participants who had a post-dose response (negative at baseline to positive at any time post baseline) for SARS-CoV-2 nucleocapsid antibodies.

There were two secondary efficacy endpoints: incidence of SARS-CoV-2 RT-PCR–positive severe or critical illness occurring post dose, and incidence of Covid-19–related emergency room (ER) visits occurring post dose. Severe Covid-19 was characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia (oxygen saturation [SpO_2] <90% in room air or severe respiratory distress) and a World Health Organization (WHO) Clinical Progression Scale[1] score of 5 or higher (Table S7) prior to unblinding or vaccination.

The secondary pharmacokinetic endpoint was measurement of serum AZD7442 concentrations. Exploratory endpoints were post-dose geometric mean titers of

SARS-CoV-2 neutralizing antibodies after a single IM dose of AZD7442, and genotypic analysis of SARS-CoV-2 variants.

A post hoc analysis of primary efficacy endpoint events (first post-dose occurrence of SARS-CoV-2 RT-PCR–positive symptomatic illness) was performed in which the efficacy observed within the first 3 months (0–3-month time period) was compared with the efficacy observed within the 3–6-month time period.

A post hoc analysis of the number of participants hospitalized due to Covid-19, regardless of prior vaccination or unblinding, was performed for the primary and median 6-month follow-up analyses.

Serum sampling and bioanalytical analyses

Serum samples for anti-nucleocapsid antibody, neutralizing antibody, and AZD7442 pharmacokinetic assessments were collected predose and at days 8, 29, 58, 92, and 183. Samples will also be collected at days 366 (scheduled) and 457 (optional) for neutralizing antibody and AZD7442 pharmacokinetic assessments. For participants who developed Covid-19, serum samples for neutralizing antibody and AZD7442 pharmacokinetic assessments were collected at illness visit days 1, 14, 21, and 28.

SARS-CoV-2 nucleocapsid antibodies were measured for all participants using the Elecsys® anti-SARS-CoV-2 nucleocapsid serology test (Roche Diagnostics, Vienna, Austria), an electroluminescence immunoassay-based modality that allows for the qualitative detection of IgG reactive to the SARS-CoV-2 nucleoprotein in human serum. Anti–SARS-CoV-2 specific antibodies were captured to streptavidin-coated solid phase microparticles with biotinylated SARS-CoV-2–specific antigen and qualitative results were determined via a two-point calibration and a cutoff formula.

The assay was validated and performed by LabCorp Drug Development (Indianapolis, IN, USA).

Neutralizing antibody titers against SARS-CoV-2 were assessed in serum samples collected in a validated live neutralization assay (plaque reduction neutralization test $[PRNT]_{80}$) by Viroclinics Biosciences (Rotterdam, Netherlands), after administration of AZD7442, as described previously.[2]

Serum samples were analyzed for tixagevimab and cilgavimab concentrations by PPD Laboratories (Richmond, VA, USA) using a validated ultra-high performance liquid chromatography method coupled with tandem mass spectrometry with positive electrospray. As previously described, 20 -µL samples were diluted and extracted with streptavidin magnetic beads coated with biotinylated SARS-CoV-2 receptor-binding domain. Isolated analytes were digested (denaturation, reduction, alkylation, and trypsin digestion) and the extract fortified with stable isotope-labeled peptide internal standard working solution. Unknown samples were quantified using a linear, 1/concentration² weighted, least-squares regression algorithm.[2]

Sequencing of SARS-CoV-2 samples

The full-length viral spike gene (AA 1-1274) was amplified from SARS-CoV-2 RT-PCR–positive nasopharyngeal swabs collected at illness visits using a standard, single-tube population-based RT-PCR method and sequenced in a validated GenoSure SARS-CoV-2 spike next-generation sequencing assay at Monogram Biosciences (South San Francisco, CA, USA). Sequence files were analyzed to determine frequency of amino acid polymorphisms (consensus; reported at ≥25% frequency). For participants who developed SARS-CoV-2 RT-PCR–positive

symptomatic illness, SARS-CoV-2 spike protein sequences were available on illness visit days 1 or 14.

The Pango dynamic nomenclature is a system for identifying and naming distinct SARS-CoV-2 lineages of epidemiological relevance, based on SARS-CoV-2 whole genome sequences.[3,4] A spike-only version of the Pangolin Covid-19 lineage assigner (Hedgehog), under development by the academic developers of Pangolin at the University of Edinburgh and Oxford University (https://github.com/aineniamh/hedgehog), was used to classify SARS-CoV-2 spike sequences from the PROVENT study to current Pango lineages (version 1.2.6) or sets of lineages.[5]

Statistical analysis

Hypotheses and sample size

The null hypothesis for the primary endpoint was: efficacy (calculated as 1 – relative risk) of AZD7442 compared to placebo in preventing Covid-19 is equal to 0. The alternative hypothesis was: efficacy of AZD7442 compared to placebo in preventing Covid-19 is not equal to 0.

Version 7 of the protocol amended the timing of the primary analysis to occur after approximately 24 primary endpoint events were observed or 30% of trial participants elected to become unblinded. The statistical rationale for this protocol amendment was an observed increase in unblinding rate in the study population, which indicated that event accrual would slow significantly owing to unblinding and vaccination, and also that power for one of the key supportive estimands (intent-to-treat analysis without censoring) would decrease owing to vaccine efficacy. The 30% unblinding

value was therefore chosen to achieve reporting in a timely manner, providing an analysis estimating the treatment effect in the randomized target population with relevant congruency between the primary and supportive estimands. Simulations were performed using the overall observed rates of unblinding and primary endpoint events across arms, an assumed AZD7442 efficacy of 80%, and an assumed Covid-19 vaccine efficacy of 90% against symptomatic Covid-19.[6-10]

For analysis of the primary efficacy endpoint, a study population of approximately 5150 participants randomized in a 2:1 ratio with a minimum of 18 observed events, assuming 80% true efficacy and 0.74% observed attack rate in the placebo arm at the time of the analysis, was estimated to provide approximately 90% power to demonstrate the lower bound of the two-sided 95% confidence interval (CI) for efficacy to be >0.

Given the variable follow-up that would be available at the primary analysis, the attack rates used in sample size determination and power calculations used an observed attack rate based on expected follow-up rather than an annualized attack rate. Ten thousand simulations of trials were performed to estimate power, using Poisson regression model with robust variance, with no participants lost to follow-up.[11]

Statistical methods

Demographics and baseline clinical characteristics analyses used the full analysis set (FAS): all participants who were randomized and received at least one of the two planned injections, with a full dose being two injections. Participants were classified according to their randomized study drug regardless of what was actually received.

The primary and secondary efficacy analyses used the full pre-exposure analysis set (FPAS): all participants in the FAS who did not have a prior SARS-CoV-2 RT-PCR–positive confirmed Covid-19 infection. Participants were classified according to their randomized study drug regardless of what was actually received.

The safety analyses used the safety analysis set (SAS): all participants who were randomized and received at least one of the two planned injections. Participants were classified according to study drug received.

The pharmacokinetic analyses used the pharmacokinetic analysis set: all participants who were randomized and received at least one injection of AZD7442 and from whom blood samples were assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum pharmacokinetic observation post dose. A dose was two injections (one tixagevimab and one cilgavimab injection) as per the protocol. Participants receiving placebo were not included in these analyses.

Statistical tests

Statistical tests were conducted at the two-sided 5% significance level; 95% CIs were two-sided. The primary analysis used a while-on-treatment estimand strategy, in which data from participants whose randomized assignment was unblinded or from participants who received a Covid-19 vaccine were censored at the date of unblinding or vaccine administration, whichever was earlier. Participants without events prior to day 183 were censored at the earlier date of study discontinuation or data cutoff date. All deaths were independently determined to be related or not

related to Covid-19 by the external MAC. Deaths that were adjudicated as related to Covid-19 were included as a primary efficacy endpoint event.

The primary efficacy endpoint was a binary response, whereby a participant's status was classified as symptomatic Covid-19 or not prior to day 183.

A Poisson regression model with robust variance was used as the primary efficacy analysis model to estimate the relative risk of symptomatic infection in the AZD7442 group compared with the placebo group. The model included group (AZD7442 versus placebo) and age at informed consent (≥60 years versus <60 years) as covariates, with the log of the follow-up time used as an offset. An unstructured correlation matrix was specified for the model. For participants who met the primary endpoint before day 183, follow-up was calculated as (date of onset of primary endpoint) – (date of dosing) + 1. For participants who did not experience a primary endpoint event before day 183, efficacy follow-up time was considered censored and calculated as (date of end of study or date of last assessment, whichever is later) – (date of dosing) + 1. End of study dates occurring after day 183 were censored at day 183.

Efficacy was calculated as relative risk reduction (RRR) = 100% × (1 – relative risk), which was the incidence of infection in the AZD7442 group relative to that in the placebo group, expressed as a percentage.

To support the primary analysis, a Cox proportional hazard model giving the hazard ratio (HR) was fitted to the data, along with Kaplan-Meier curves for the active and control groups, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR–positive symptomatic illness occurring post dose and prior to day 183.

There was no evidence of violation of the proportional hazard assumption following evaluation of log-log survival curves and through fitting time-dependent covariates.

Two key supportive analyses were prespecified in the study protocol and included in the multiple testing framework to control the type I error rate. The first key supportive analysis of the primary efficacy endpoint used a treatment policy estimand strategy, in which data from participants whose randomized assignment was unblinded or from participants who received a Covid-19 vaccine were included and analyzed regardless of their unblinding or vaccination status. The endpoint definition was expanded to include deaths from any cause post dose of AZD7442 or placebo and prior to day 183 in the second key supportive analysis.

For missing data, participants who discontinued early from the study or were lost to follow-up before experiencing a primary endpoint event were censored in the Kaplan -Meier and Poisson regression analyses. Censoring due to loss to follow up or early discontinuation was considered to be noninformative. Participants who were unblinded or vaccinated before experiencing a primary endpoint event were censored in the Kaplan -Meier and Poisson regression analyses. Censoring arising from unblinding or vaccination was considered independent censoring (i.e., censoring was noninformative within the subgroup of interest). A key supportive analysis using an intent-to-treat policy in which unblinding or vaccination did not result in censoring (unblinding or vaccination event ignored) was conducted to assess the impact of independent censoring (Table 3).

A hierarchical approach was used to control for multiplicity of the primary, key supportive, and key secondary analyses on the basis of a two-sided alpha level

of 0.05. The hierarchical approach at the primary analysis was conducted in the following order:

1. Primary efficacy endpoint analyzed using the while-on-treatment estimand.
2. First key supportive analysis: primary efficacy endpoint analyzed using the treatment policy estimand.
3. second key supportive analysis: primary endpoint definition expanded to include death due to any cause (using the while-on-treatment estimand).
4. key secondary efficacy endpoint.

Statistical significance of the primary, key supportive, and key secondary efficacy analyses was considered achieved if the observed P value was <0.05. No statistical testing was performed for the safety endpoints.

Supplementary results

Missing data analysis

Missing data frequency was small and balanced between treatment arms (Table S2). Participant demographics and baseline clinical characteristics were generally balanced between censoring subgroups (Table S3). Increased censoring due to unblinding or vaccination was seen in participants aged ≥60, likely reflecting prioritization of this age group for Covid-19 vaccination.

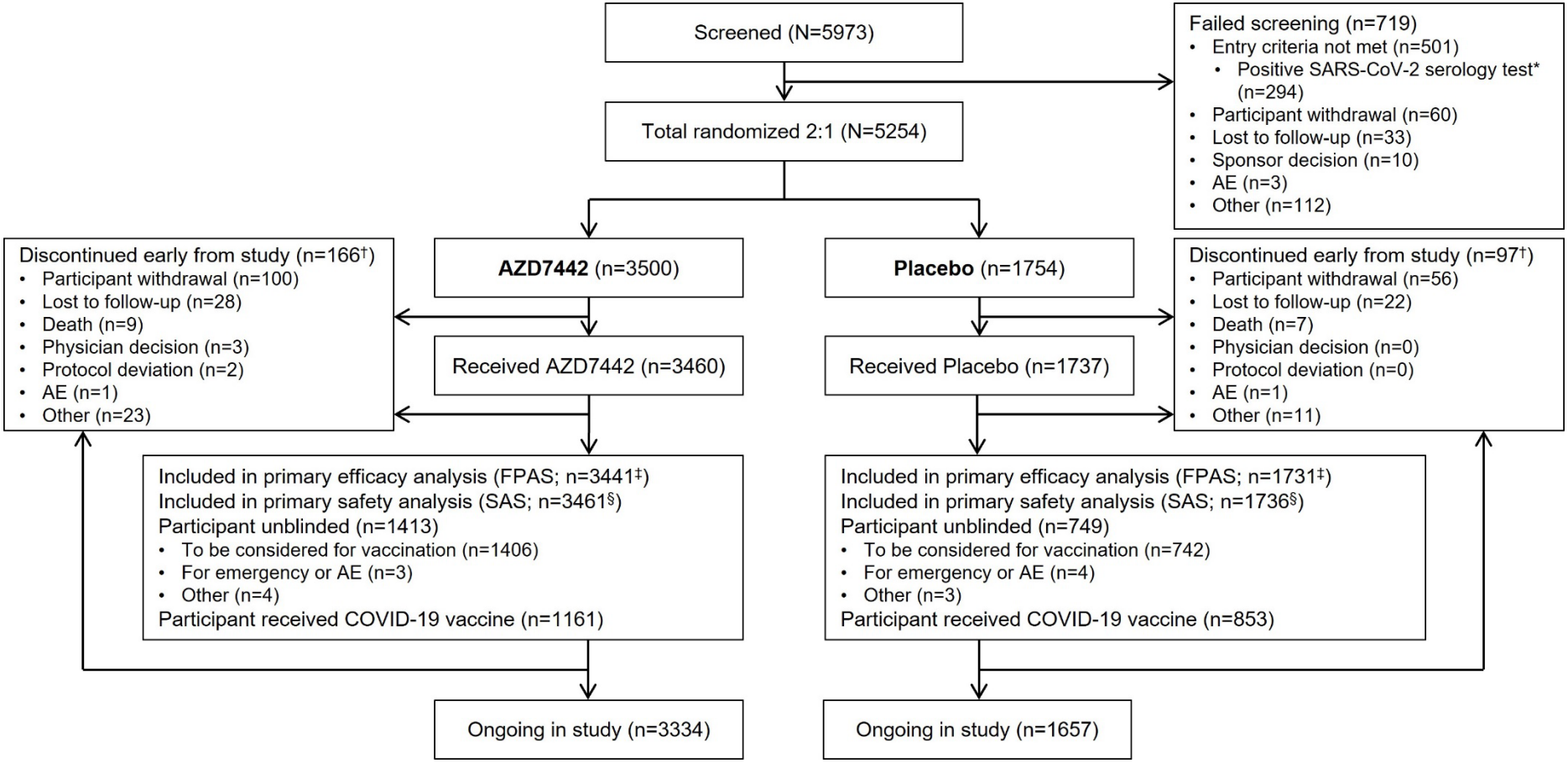
Covid-19–related hospitalizations

At the time of the primary data cut, 0 and 3 (0.2%) participants in the AZD7442 and placebo groups, respectively, had been hospitalized due to Covid-19, regardless of prior vaccination or unblinding.

At the time of the median 6-month follow-up data cut, 0 and 7 (0.4%) participants in the AZD7442 and placebo groups, respectively, had been hospitalized due to Covid-19, regardless of prior vaccination or unblinding.

Supplementary figures

Figure S1. Participant flow through trial (CONSORT flow diagram)



*Screening failed because of inclusion criterion 4: A negative result from point-of-care SARS-CoV-2 serology testing at screening, using the FaStep Assure tech Point-of-Care (POC)/Fingerstick Fastep® Covid-19 IgG/IgM Rapid Test Device (Assure Tech, Hangzhou, China).

†Includes 40 participants in the AZD7442 group and 17 in the placebo group who discontinued from the study before dosing. All participants who discontinued at any time after dosing were included in the SAS. Participants who discontinued after dosing were included in the FPAS if they had a negative SARS-CoV-2 RT-PCR test at baseline.

‡Nineteen participants in the AZD7442 group and 6 in the placebo group had a positive SARS-CoV-2 RT-PCR test at baseline and per study protocol were excluded from the FPAS.

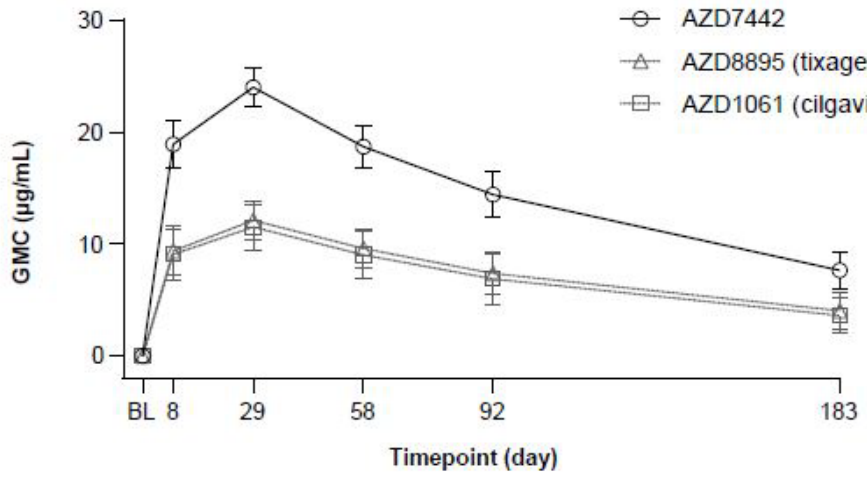
§One participant was randomized to placebo and incorrectly received AZD7442; per study protocol this participant was assessed in the AZD7442 group for the SAS.

In the PROVENT FPAS study population, 3430 and 1700 participants in the AZD7442 and placebo groups, respectively, did not have a primary endpoint event (SARS-CoV-2 RT-PCR–positive symptomatic illness). A breakdown of how participants who did not meet the primary endpoint were censored (not observed to have event; lost to follow up/early discontinuation; censored due to unblinding; censored due to vaccination) is available in Table S2. A comparison of participant characteristics between censoring categories is available in Table S3.

AE, adverse event; Covid-19, coronavirus disease 2019; FPAS, full pre-exposure analysis set; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAS, safety analysis set.

Figure S2. Pharmacokinetic and anti–SARS-CoV-2 neutralizing antibody analyses: (A) serum AZD7442 geometric mean concentration ± SD, and (B) SARS-CoV-2 neutralizing antibody geometric mean titers with 95% CI

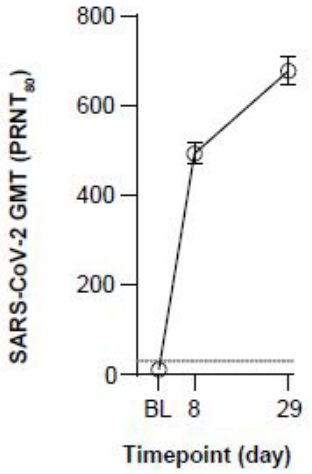
A



No. participants at visit

AZD7442	1776	1464	1139	1037	639	322
AZD1061	1776	1464	1141	1034	638	322
AZD8895	1776	1464	1141	1037	639	322

B



No. participants at visit	1025	928	998

Per protocol, all participants who received AZD7442 and from whom PK blood samples were assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post dose were included in the pharmacokinetic analysis set.

(A) Values are GMC ± gSD. Individual serum concentrations with levels <LLOQ were set to 50% of LLOQ (0.3 µg/mL). Individual serum concentrations that were not reportable (NR) were reported as NR and missing values were reported as no sample (NS); any values reported as NR or NS were excluded from analysis. Of the 3500 randomized participants who received AZD7442, 1607 (45.9%) did not have evaluable plasma concentration data at the time of this analysis, 40 (1.1%) were not dosed, and 1 (<0.1%) had an exclusionary protocol violation at baseline.

(B) Values are GMT with 95% CI. Data were only available for 43 and 6 participants at days 58 and 92, respectively, and so are not reported here. The dashed line represents the GMT of neutralizing antibody from 28 convalescent plasma samples from patients with Covid-19.[2] Of the 3500 randomized participants who received AZD7442, 2389 (68.3%) did not have evaluable plasma concentration data at the time of this analysis, 40 (1.1%) were not dosed, and 1 (<0.1%) had an exclusionary protocol violation at baseline.

BL, baseline; CI confidence interval; gSD, geometric standard deviation; GMC, geometric mean concentration; GMT, geometric mean titer; LLOQ, lower limit of quantification; PK, pharmacokinetics; PRNT, plaque reduction neutralization test; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Supplementary tables

Table S1. Definition of symptomatic Covid-19 (qualifying symptoms)

Participant must present with at least one of the following symptoms:	
No minimum duration	**Must be present for ≥2 days**
Fever	Runny nose
Shortness of breath	Congestion
Difficulty breathing	New loss of smell
New onset confusion (only for participants ≥60 years old)	New loss of taste
Appetite loss or decreased food intake (only for participants ≥60 years old)	Headache
Increased supplemental oxygen requirement (only for participants ≥60 years old on baseline supplemental oxygen)	Sore throat
	Body aches
	Chills
	Cough
	Diarrhea
	Muscle aches
	Fatigue
	Nausea
	Vomiting

Covid-19, coronavirus disease 2019.

Table S2. Censoring category breakdown for primary endpoint

Category	AZD7442	Placebo
SARS-CoV-2 RT-PCR–positive symptomatic illness (primary endpoint event), n/N (%)	11/3441 (0.3)	31/1731 (1.8)
Did not have primary endpoint event (FPAS: censored participants), N	**3430**	**1700**
Not observed to have event, n (%)	1549 (45.2)	713 (41.9)
Lost to follow up/early discontinuation, n (%)	83 (2.4)	37 (2.2)
Censored due to unblinding, n (%)	1346 (39.2)	688 (40.5)
Censored due to vaccination, n (%)*	452 (13.2)	262 (15.4)

*Some participants were vaccinated without unblinding.

FPAS, full pre-exposure analysis set; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S3. Participant demographics and baseline clinical characteristics by outcome category

Characteristic, n (%)	Censoring reason								Events	
	Not observed to have event (n=2262)		Lost to follow up/early discontinuation (missing) (n=120)		Censored due to unblinding (n=2034)		Censored due to vaccination (n=714)		First SARS-CoV-2 RT-PCR–positive symptomatic illness (censored at unblinding or receipt of Covid-19 vaccine) (n=42)	
	AZD7442	Placebo	AZD7442	Placebo	AZD7442	Placebo	AZD7442	Placebo	AZD7442	Placebo
Treatment group*	1549	713	83	37	1346	688	452	262	11	31
Age group										
≥60 years	535 (34.5)	248 (34.8)	26 (31.3)	16 (43.2)	695 (51.6)	360 (52.3)	237 (52.4)	119 (45.4)	3 (27.3)	12 (38.7)
<60 years	1014 (65.5)	465 (65.2)	57 (68.7)	21 (56.8)	651 (48.4)	328 (47.7)	215 (47.6)	143 (54.6)	8 (72.7)	19 (61.3)
Sex										
Male	913 (58.9)	413 (57.9)	56 (67.5)	20 (54.1)	639 (47.5)	337 (49.0)	246 (54.4)	148 (56.5)	2 (18.2)	16 (51.6)
Female	636 (41.1)	300 (42.1)	27 (32.5)	17 (45.9)	707 (52.5)	351 (51.0)	206 (45.6)	114 (43.5)	9 (81.8)	15 (48.4)
Ethnicity										
Not Hispanic/Latino	1140 (73.6)	542 (76.0)	61 (73.5)	28 (75.7)	1138 (84.5)	580 (84.3)	373 (82.5)	231 (88.2)	9 (81.8)	25 (80.6)
Hispanic/Latino	335 (21.6)	128 (18.0)	16 (19.3)	8 (21.6)	119 (8.8)	52 (7.6)	59 (13.1)	22 (8.4)	2 (18.2)	5 (16.1)
Not reported/ unknown	74 (4.8)	43 (6.0)	6 (7.2)	1 (2.7)	89 (6.6)	56 (8.1)	20 (4.4)	9 (3.4)	0	1 (3.2)
Race										
White	962 (62.1)	405 (56.8)	54 (65.1)	30 (81.1)	1169 (86.8)	597 (86.8)	338 (74.8)	187 (71.4)	10 (90.9)	24 (77.4)
Black/African American	417 (26.9)	212 (29.7)	20 (24.1)	4 (10.8)	79 (5.9)	34 (4.9)	77 (17.0)	48 (18.3)	0	4 (12.9)

Other†	170 (11.0)	96 (13.5)	9 (10.8)	3 (8.1)	98 (7.3)	57 (8.3)	37 (8.2)	27 (10.3)	1 (9.1)	3 (9.7)
SARS-CoV-2 status at baseline										
Positive	0	0	0	0	0	0	0	0	0	0
Negative	1485 (95.9)	683 (95.8)	80 (96.4)	36 (97.3)	1312 (97.5)	669 (97.2)	447 (98.9)	255 (97.3)	11 (100)	30 (96.8)
Missing	64 (4.1)	30 (4.2)	3 (3.6)	1 (2.7)	34 (2.5)	19 (2.8)	5 (1.1)	7 (2.7)	0	1 (3.2)
High risk for severe Covid-19 at baseline										
Any	1187 (76.6)	567 (79.5)	65 (78.3)	27 (73.0)	1044 (77.6)	534 (77.6)	349 (77.2)	210 (80.2)	11 (100)	21 (67.7)
Obesity (BMI ≥30 kg/m^2)	617 (39.8)	278 (39.0)	33 (39.8)	16 (43.2)	598 (44.4)	294 (42.7)	195 (43.1)	106 (40.5)	7 (63.6)	14 (45.2)
Hypertension	538 (34.7)	275 (38.6)	32 (38.6)	9 (24.3)	469 (34.8)	236 (34.3)	184 (40.7)	104 (39.7)	4 (36.4)	10 (32.3)
Smoking	430 (27.8)	204 (28.6)	29 (34.9)	9 (24.3)	179 (13.3)	99 (14.4)	76 (16.8)	53 (20.2)	2 (18.2)	5 (16.1)
Diabetes	212 (13.7)	106 (14.9)	12 (14.5)	5 (13.5)	178 (13.2)	93 (13.5)	83 (18.4)	35 (13.4)	1 (9.1)	3 (9.7)
Asthma	130 (8.4)	66 (9.3)	8 (9.6)	2 (5.4)	184 (13.7)	98 (14.2)	53 (11.7)	29 (11.1)	2 (18.2)	3 (9.7)

* Participants were randomized 2:1 to AZD7442 and placebo

†Includes participants identifying as Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander, and unknown/not reported/multiple/missing data.

BMI, body mass index; Covid-19, coronavirus disease 2019; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S4. Representativeness of study participants

Category	Example
Disease, problem, or condition under investigation	SARS-CoV-2 infection; Covid-19
Special considerations related to:	
Sex and gender	Higher Covid-19 case fatality rates have been reported for male sex compared with female sex in some countries, which may be impacted by additional variables such as infection/exposure risk and comorbidities.
Age	Older age is associated with more severe Covid-19 outcomes and death.
Race or ethnic group	Black, Latino, and other ethnic/racial groups are disproportionately affected by Covid-19 in countries including the United States and United Kingdom.
Geography	Covid-19 prevalence has been variable throughout the world depending on regional/country social distancing measures, travel restrictions, and vaccination rates.
Other considerations	Medical comorbidities, including diabetes, cardiovascular disease, and obesity, are associated with more severe Covid-19 outcomes. Risk of SARS-CoV-2 exposure and infection can be affected by location or circumstance, such as health care workers, military personnel in high -density settings, and workers in industrial settings.
Overall representativeness of this trial	The participants in the present study demonstrated a high proportion of adults aged ≥60 years (43% overall) and individuals with comorbidities placing them at high risk of severe Covid-19 (78%). Overall, 53% of participants in the study were considered at increased risk of exposure to SARS-CoV-2. The proportion of Hispanic/Latino participants (15%) was representative of the US population. Overall, 17% of participants were Black or African American, representing a slightly higher proportion than Black populations in the US and UK. The proportion of Asian participants in the study overall (3%) appears slightly lower than the proportion of Asian populations within the US and UK, and the proportion of American Indian/Alaska Native participants (0.6%) was also lower compared with the proportion among the US population.

Potential study participants were directed to the study website to complete a set of prescreen questions to determine their pre-eligibility.

Potential participants were asked to identify their age category as “Yes, I am between 18 and 59 years of age (inclusive),” “Yes, I am 60 years of age or older,” or “No”.

Potential participants were asked prescreen questions to determine whether they had an increased risk of getting Covid-19 (due to location, employment, or personal circumstances) OR were less likely than most adults to benefit from a vaccine (e.g., due to older age, obesity, or immunosuppression from a health condition or medication).

Potential participants were asked to choose the race or ethnicity that describes them (choose all that apply): Hispanic or Latino; American Indian or Alaskan Native; Asian; Black or African American; Native Hawaiian or other Pacific Islander; White; Other; Prefer not to say.

Table S5. Number of participants with SAEs by system organ class, primary data cut (SAS)

Participants with at least one SAE, n (%)	AZD7442 (n=3461)	Placebo (n=1736)	Total (N=5197)
Any SAE	50 (1.4)	23 (1.3)	73 (1.4)
Infections and infestations*	8 (0.2)	5 (0.3)	13 (0.3)
Injury, poisoning, and procedural complications†	4 (0.1)	8 (0.5)	12 (0.2)
Nervous system disorders‡	9 (0.3)	0	9 (0.2)
Cardiac disorders§	6 (0.2)	1 (0.1)	7 (0.1)
Gastrointestinal disorders‖	6 (0.2)	1 (0.1)	7 (0.1)
Renal and urinary disorders	6 (0.2)	1 (0.1)	7 (0.1)
Musculoskeletal and connective tissue disorders	4 (0.1)	1 (0.1)	5 (0.1)
Hepatobiliary disorders	3 (0.1)	1 (0.1)	4 (0.1)
Metabolism and nutrition disorders	3 (0.1)	0	3 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	3 (0.2)	3 (0.1)
Respiratory, thoracic, and mediastinal disorders	1 (<0.1)	2 (0.1)	3 (0.1)
Vascular disorders	2 (0.1)	1 (0.1)	3 (0.1)
Blood and lymphatic system disorders	2 (0.1)	0	2 (<0.1)
Clinical laboratory tests	1 (<0.1)	1 (0.1)	2 (<0.1)
Pregnancy, puerperium, and perinatal conditions	1 (<0.1)	0	1 (<0.1)
Psychiatric disorders	1 (<0.1)	0	1 (<0.1)
Reproductive system and breast disorders	1 (<0.1)	0	1 (<0.1)

*Includes appendicitis (perforated), cellulitis, Covid-19, Covid-19 pneumonia, cystitis, diverticulitis, gastroenteritis, osteomyelitis, peritonitis, postoperative wound infection, sepsis, and staphylococcal infection.

†Includes concussion, femur fracture, fibula fracture, gunshot wound, incisional hernia (obstructive), joint injury, multiple injuries, overdose, procedural pain, subdural hemorrhage, tendon rupture, and tibia fracture.

‡Includes Bell's palsy, cerebrovascular accident, complex regional pain syndrome, metabolic encephalopathy, migraine, partial seizures, syncope, and transient ischemic attack.

§Includes acute left ventricular failure, acute myocardial infarction, myocardial infarction, and paroxysmal atrioventricular block.

‖Includes abdominal hernia, abdominal pain, acute pancreatitis, chronic pancreatitis, gastrointestinal ulcer hemorrhage, irritable bowel syndrome, and mesenteric artery thrombosis.

SAEs were coded using the Medical Dictionary for Regulatory Activities, version 24.0

Covid-19, coronavirus disease 2019; SAE, serious adverse event; SAS, safety analysis set.

Table S6. Safety data, median 6-month data cut (SAS)

Participants with at least one event, n (%)*	AZD7442 (n=3461)†	Placebo (n=1736)†	Total (N=5197)
AEs	1579 (45.6)	790 (45.5)	2369 (45.6)
Mild AEs	835 (24.1)	419 (24.1)	1254 (24.1)
Moderate AEs	596 (17.2)	295 (17.0)	891 (17.1)
Severe AEs	128 (3.7)	65 (3.7)	193 (3.7)
SAEs	130 (3.8)	58 (3.3)	188 (3.6)
Intervention-related‡ SAEs	1 (<0.1)	0	1 (<0.1)
AEs leading to study discontinuation	2 (0.1)	1 (0.1)	3 (0.1)
Medically attended AEs	641 (18.5)	280 (16.1)	921 (17.7)
AEs of special interest	92 (2.7)	37 (2.1)	129 (2.5)
Injection site reaction	82 (2.4)	36 (2.1)	118 (2.3)
Anaphylaxis	1 (<0.1)	0	1 (<0.1)
Immune complex disease§	0	0	0
Other	9 (0.3)	2 (0.1)	11 (0.2)
Intervention-related‡ AEs of special interest	87 (2.5)	36 (2.1)	123 (2.4)
All AEs with outcome of death‖	9 (0.3)	7 (0.4)	16 (0.3)
Illicit drug overdose	2 (0.1)	1 (0.1)	3 (0.1)
Narcotic toxicity¶	0	1 (0.1)	1 (<0.1)
Covid-19**	0	1 (0.1)	1 (<0.1)
Covid-19 ARDS**	0	1 (0.1)	1 (<0.1)
Septic shock	1 (<0.1)	0	1 (<0.1)
Arrhythmia	1 (<0.1)	0	1 (<0.1)
Cardio-respiratory arrest	1 (<0.1)	0	1 (<0.1)
Congestive cardiac failure	1 (<0.1)	0	1 (<0.1)
Myocardial infarction	1 (<0.1)	0	1 (<0.1)
End-stage renal disease	1 (<0.1)	0	1 (<0.1)
Renal failure	1 (<0.1)	0	1 (<0.1)
Hepatic cirrhosis	0	1 (0.1)	1 (<0.1)
Malignant neoplasm (unknown primary site)	0	1 (0.1)	1 (<0.1)
Dementia (Alzheimer's type)	0	1 (0.1)	1 (<0.1)

*Participants may have had more than one event.

†One participant was randomized to placebo and incorrectly received AZD7442; per study protocol this participant was assessed in the AZD7442 group for the SAS.

‡Events were determined to be intervention-related by investigators based on their judgment.

§Immune complex disease was removed as an AEs of special interest following adjudication.

‖All deaths were determined by the investigator to not be related to the study drug received.

¶Participant died as a result of accidental exposure to two substances controlled under Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs.[12]

**Cases were adjudicated to be Covid-19 related by the independent and external Morbidity Adjudication Committee.

AEs were coded using the Medical Dictionary for Regulatory Activities, version 24.0.

AE, adverse event; ARDS, acute respiratory distress syndrome; Covid-19, coronavirus disease 2019; SAE, serious adverse event; SAS, safety analysis set.

Table S7. Number of participants with SAEs by system organ class, median 6-month data cut (SAS)

Participants with at least one SAE, n (%)	AZD7442 (n=3461)	Placebo (n=1736)	Total (N=5197)
Any SAE	130 (3.8)	58 (3.3)	188 (3.6)
Infections and infestations*	31 (0.9)	15 (0.9)	46 (0.9)
Cardiac disorders†	23 (0.7)	5 (0.3)	28 (0.5)
Nervous system disorders‡	18 (0.5)	5 (0.3)	23 (0.4)
Injury, poisoning, and procedural complications§	11 (0.3)	12 (0.7)	23 (0.4)
Gastrointestinal disorders‖	12 (0.3)	6 (0.3)	18 (0.3)
Hepatobiliary disorders	8 (0.2)	5 (0.3)	13 (0.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5 (0.1)	7 (0.4)	12 (0.2)
Renal and urinary disorders	8 (0.2)	1 (0.1)	9 (0.2)
Respiratory, thoracic, and mediastinal disorders	5 (0.1)	4 (0.2)	9 (0.2)
Psychiatric disorders	5 (0.1)	3 (0.2)	8 (0.2)
Vascular disorders	4 (0.1)	4 (0.2)	8 (0.2)
Metabolism and nutrition disorders	6 (0.2)	0	6 (0.1)
Musculoskeletal and connective tissue disorders	5 (0.1)	1 (0.1)	6 (0.1)
General disorders and administration site conditions	2 (0.1)	3 (0.2)	5 (0.1)
Clinical laboratory tests	3 (0.1)	1 (0.1)	4 (0.1)
Blood and lymphatic system disorders	2 (0.1)	0	2 (<0.1)
Reproductive system and breast disorders	2 (0.1)	0	2 (<0.1)
Pregnancy, puerperium, and perinatal conditions	1 (<0.1)	0	1 (<0.1)
Skin and subcutaneous tissue disorders	1 (<0.1)	0	1 (<0.1)
Ear and labyrinth disorders	0	1 (0.1)	1 (<0.1)
Eye disorders	0	1 (0.1)	1 (<0.1)

*Includes abdominal abscess, abscess limb, appendicitis, arteriovenous graft site infection, cellulitis, Covid-19, Covid-19 pneumonia, cystitis, device related infection, diverticulitis, enterococcal bacteremia, gastroenteritis, influenza, localized infection, lower respiratory tract infection, lung abscess, osteomyelitis, peritonitis, pneumonia, postoperative wound infection, sepsis, septic shock, sialadenitis, soft tissue infection, staphylococcal infection, urinary tract infection, and urosepsis.

†Includes acute left ventricular failure, angina pectoris, arrhythmia, arteriosclerosis coronary artery, atrial fibrillation, cardiac failure, cardiomegaly, cardiomyopathy, cardio-respiratory arrest, congestive cardiac failure, coronary artery disease, myocardial infarction, and paroxysmal atrioventricular block.

‡Includes Bell's palsy, carotid artery stenosis, cerebral infarction, cerebrovascular accident, complex regional pain syndrome, dementia Alzheimer's type, dizziness, epilepsy, hepatic encephalopathy, lacunar infarction, loss of consciousness, metabolic encephalopathy, migraine, partial seizures, presyncope, ruptured cerebral aneurysm, seizure, syncope, and transient ischemic attack.

§Includes ankle fracture, concussion, fall, femur fracture, fibula fracture, gunshot wound, incisional hernia, joint injury, lower limb fracture, multiple injuries, overdose, peritoneal dialysis complication, procedural pain, road traffic accident, skin laceration, subdural hemorrhage, tendon rupture, tibia fracture, toxicity to various agents, and wound.

‖Includes abdominal hernia, abdominal pain, acute pancreatitis, diarrhea, discolored feces, esophageal hemorrhage, gastric ulcer, gastritis, gastrointestinal hemorrhage, gastrointestinal ulcer hemorrhage, hemorrhoids, irritable bowel syndrome, mesenteric artery thrombosis, pancreatitis, peritoneal cyst, small intestinal obstruction, and vomiting.

SAEs were coded using the Medical Dictionary for Regulatory Activities, version 24.0.

Covid-19, coronavirus disease 2019; SAE, serious adverse event; SAS, safety analysis set.

Table S8. Key secondary efficacy endpoint

Endpoint	Primary analysis		Median 6-month follow-up*	
	AZD7442	Placebo	AZD7442	Placebo
Key secondary: Post-dose SARS-CoV-2 nucleocapsid antibody–positive (censored at unblinding or receipt of Covid-19 vaccine)†				
N	3123	1564	3121	1564
n (%)	21 (0.7)	21 (1.3)	38 (1.2)	42 (2.7)
RRR (95% CI)	51.1% (10.6–73.2)		57.7% (34.7–72.7)	
P value	0.020		—	

*Analysis not prespecified in protocol; P values not computed.

†Defined as seronegative at baseline and seropositive at any time post baseline. Antibody testing was conducted at prespecified study days and was not dependent on participants reporting symptoms of Covid-19.

Estimates were based on a Poisson regression with robust variance, with the model including group (AZD7442 versus placebo) and age at informed consent (≥60 years versus <60 years), with the log of the follow-up time as an offset.

Estimated RRR >0 provides evidence in favor of AZD7442 with P<0.05 indicating statistical significance.

Percentages were based on the number of participants in the analysis by group (N).

CI, confidence interval; Covid-19, coronavirus disease 2019; RRR, relative risk reduction; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S9. Definition of SARS-CoV-2 RT-PCR–positive severe or critical illness

Either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates), or hypoxemia (SpO_2 <90% or severe respiratory distress), plus a WHO Clinical Progression Scale [below] score of ≥5 prior to unblinding or vaccination		
WHO Clinical Progression Scale		
Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory: mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation; pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation; pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation; pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Death	10

*If hospitalized for isolation only, status recorded as for ambulatory patient.

The WHO Clinical Progression Scale provides a measure of illness severity across a range from 0 (not infected) to 10 (dead).[1]

ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; NIV, noninvasive ventilation; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation; WHO, World Health Organization.

Table S10. Post hoc analysis of primary efficacy endpoint events (first SARS-CoV-2 RT-PCR–positive symptomatic illness, censored at unblinding or receipt of Covid-19 vaccine)

	Time period			
	0–3 months		3–6 months	
	AZD7442	Placebo	AZD7442	Placebo
N	3441	1731	2003	960
n (%)	8 (0.2)	19 (1.1)	3 (0.1)	12 (1.2)
RRR (95% CI)	79% (52–91)		88% (58–97)	

Estimated RRR >0 provides evidence in favor of AZD7442. The analysis was not prespecified in the study protocol, so P values were not computed.

Estimates were based on a Poisson regression with robust variance, with the model including group (AZD7442 versus placebo) and age at informed consent (≥60 years versus <60 years), with the log of the follow-up time as an offset.

Percentages were based on the number of participants in the analysis by group (N).

CI, confidence interval; Covid-19, coronavirus disease 2019; RRR, relative risk reduction; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table S11. Summary of detected SARS-CoV-2 spike-based lineages, median 6-month data cut

SARS-CoV-2 spike-based lineage*	Participants with data, n (%)		
	AZD7442 (n=11)	Placebo (n=31)	Total (n=42)
B.1.1.7_1 (Alpha†)	0	5 (11.9)	5 (11.9)
B.1.351 (Beta†)	1 (2.4)	0	1 (2.4)
B.1.617.2‡ (Delta§)	0	5 (11.9)	5 (11.9)
A_1	1 (2.4)	0	1 (2.4)
A_22	1 (2.4)	2 (4.8)	3 (7.1)
AY.3.1	1 (2.4)	0	1 (2.4)
B.1.1.315_1	1 (2.4)	0	1 (2.4)
B.1.429‖	2 (4.8)	0	2 (4.8)
B.1.526¶	0	1 (2.4)	1 (2.4)
RNA insufficient for sequencing	4 (9.5)	18 (42.8)	22 (52.4)

*Lineage nomenclature from WHO. The Omicron variant (currently circulating VoC), Gamma variant (previously circulating VoC), and the Zeta, Eta, Theta, Kappa, Lambda, and Mu variants (previously circulating VoIs) were not identified in the PROVENT study population.[13]

†The Alpha and Beta variants were designated as currently circulating VoCs during the PROVENT study and were redesignated as previously circulating VoCs as of March 9, 2022.

‡Includes subvariants B.1.617.2_1, _2, _3, and _4.

§The Delta variant was designated as a current circulating VoC on May 11, 2021.

‖Former VoI Epsilon; designated as previously circulating VOI as of July 6, 2021.

¶Former VoI Iota; designated as previously circulating VOI as of September 20, 2021.

All dates correct as of April 5, 2022.

QNS, quantity not sufficient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VoC, Variant of Concern; VoI, Variant of Interest; VUM; Variant Under Monitoring; WHO, World Health Organization.

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