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AZD7442 (Tixagevimab/Cilgavimab) for Post-Exposure Prophylaxis of Symptomatic Coronavirus Disease 2019

Myron J. Levin,[1] Andrew Ustianowski,[2] Steven Thomas,[3] Alison Templeton,[4] Yuan Yuan,[3] Seth Seegobin,[4] Catherine F. Houlihan,[5,6] Ibrahim Menendez-Perez,[7] Simon Pollett,[8,9] Rosalinda H. Arends,[10] Rohini Beavon,[11] Kanika Dey,[12] Pedro Garbes,[12] Elizabeth J. Kelly,[13] Gavin C. K. W. Koh,[11] Stefan Ivanov,[14] Karen A. Near,[12] Audrey Sharbaugh,[15] Katie Streicher,[13] Menelas N. Pangalos,[16] and Mark T. Esser[17]; for the COVID-19 Study to Optimally Reduce Morbidity in CareHomes and Sites with Enhanced Risk (STORMCHASER) Study Group

[1]University of Colorado Denver School of Medicine, Aurora, Colorado, USA; [2]North Manchester General Hospital, Manchester, United Kingdom; [3]Biometrics, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Gaithersburg, Maryland, USA; [4]Biometrics, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Cambridge, United Kingdom; [5]Department of Clinical Virology, University College London Hospitals National Health Service Foundation Trust, London, United Kingdom; [6]Department of Infection and Immunity, University College London, London, United Kingdom; [7]Project 4 Research, Miami, Florida, USA; [8]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA; [9]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc, Bethesda, Maryland, USA; [10]Clinical Pharmacology and Quantitative Pharmacology, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Gaithersburg, Maryland, USA; [11]Clinical Development, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Cambridge, United Kingdom; [12]Clinical Development, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Gaithersburg, Maryland, USA; [13]Translational Medicine, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Gaithersburg, Maryland, USA; [14]Clinical Development, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden; [15]Clinical Development, Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Durham, North Carolina, USA; [16]BioPharmaceuticals Research and Development, AstraZeneca, Cambridge, United Kingdom; and [17]Vaccines and Immune Therapies, BioPharmaceuticals Research and Development, AstraZeneca, Gaithersburg, Maryland, USA

(See the Editorial Commentary by Davis and Li on pages 1257–9.)

Background. This phase 3 trial assessed AZD7442 (tixagevimab/cilgavimab) for post-exposure prophylaxis against symptomatic coronavirus disease 2019 (COVID-19).

Methods. Adults without prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or COVID-19 vaccination were enrolled within 8 days of exposure to a SARS-CoV-2–infected individual and randomized 2:1 to a single 300-mg AZD7442 dose (one 1.5-mL intramuscular injection each of tixagevimab and cilgavimab) or placebo. Primary end points were safety and first post-dose SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR)–positive symptomatic COVID-19 event before day 183.

Results. A total of 1121 participants were randomized and dosed (AZD7442, n = 749; placebo, n = 372). Median (range) follow-up was 49 (5–115) and 48 (20–113) days for AZD7442 and placebo, respectively. Adverse events occurred in 162 of 749 (21.6%) and 111 of 372 (29.8%) participants with AZD7442 and placebo, respectively, mostly mild/moderate. RT-PCR–positive symptomatic COVID-19 occurred in 23 of 749 (3.1%) and 17 of 372 (4.6%) AZD7442- and placebo-treated participants, respectively (relative risk reduction, 33.3%; 95% confidence interval [CI], −25.9 to 64.7; $P = .21$). In predefined subgroup analyses of 1073 (96%) participants who were SARS-CoV-2 RT-PCR–negative (n = 974, 87%) or missing an RT-PCR result (n = 99, 9%) at baseline, AZD7442 reduced RT-PCR–positive symptomatic COVID-19 by 73.2% (95% CI, 27.1 to 90.1) vs placebo.

Conclusions. This study did not meet the primary efficacy end point of post-exposure prevention of symptomatic COVID-19. However, analysis of participants who were SARS-CoV-2 RT-PCR–negative or missing an RT-PCR result at baseline support a role for AZD7442 in preventing symptomatic COVID-19.

Clinical Trials Registration. NCT04625972.

Keywords. COVID-19; AZD7442; monoclonal antibodies; post-exposure prophylaxis; SARS-CoV-2.

Post-exposure prophylaxis comprises interventions aimed at reducing the risk of developing symptomatic disease or disease progression, as well as transmission, after pathogen exposure. Post-exposure prophylaxis is routinely recommended following exposure to viruses including influenza virus [1], human immunodeficiency virus [2], varicella-zoster virus [3], and hepatitis B virus [4].

Despite effectiveness of coronavirus disease 2019 (COVID-19) vaccines in reducing symptomatic disease, hospitalization, and mortality [5, 6], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission continues,

particularly with the emergence of highly transmissible variants [7, 8]. The risk of SARS-CoV-2 outbreak and exposure is high in settings where close indoor contact is common, such as long-term care facilities (LTCFs), healthcare facilities, and industrial and military settings, where such outbreaks have been reported even among populations with high vaccination uptake [9–11]. In these instances, additional interventions to rapidly protect individuals following SARS-CoV-2 exposure are needed, particularly for unvaccinated individuals and those at high risk of developing severe disease following infection. The median incubation period of wild-type SARS-CoV-2, from exposure to symptom onset, is estimated to be 5.1 days, and 97.5% of those who develop symptoms will do so within 11.5 days of infection [12], although this timing is likely shorter for the Omicron variant (approximately 3 days) [13]. The post-exposure period represents a potential opportunity for post-exposure prophylaxis to prevent symptomatic COVID-19.

SARS-CoV-2 neutralizing monoclonal antibodies (mAbs) represent a potential option for rapid, passive immunoprophylaxis. AZD7442 is a combination of 2 extended half-life SARS-CoV-2–neutralizing mAbs (tixagevimab and cilgavimab) derived from potent antibodies isolated from B cells from SARS-CoV-2–infected individuals. Tixagevimab and cilgavimab bind to distinct epitopes of the viral spike protein receptor-binding domain [14–17]. AZD7442 neutralizes SARS-CoV-2 and variants including Omicron [18–20] in vitro. AZD7442 significantly prevented development of symptomatic COVID-19 when used as pre-exposure prophylaxis in the phase 3 prophylaxis prevention (PROVENT) trial, protected against severe disease and death as treatment for mild to moderate COVID-19 in the phase 3 treating acute COVID-19 condition with a long half-life engineeredantibody (TACKLE) trial, and showed a 30% reduction in all-cause mortality as treatment for severe COVID-19 in the phase 3 ACTIV-3 (Therapeutics for Inpatients with COVID-19; TICO) trial, and was well tolerated across trials [21–23]. The phase 3 COVID-19 Study to Optimally Reduce Morbidity in CareHomes and Sites with Enhanced Risk (STORM CHASER) trial was conducted to assess AZD7442 for post-exposure prevention of symptomatic COVID-19 in adults within 8 days of exposure to an individual with laboratory-confirmed SARS-CoV-2 infection.

METHODS

Study Design and Participants

STORM CHASER is an ongoing, 15-month, phase 3, randomized, double-blind, placebo-controlled, multicenter study, performed at 59 sites across the United States and the United Kingdom. Data are presented from the primary analysis, assessed 30 days after the 25th primary end point event had occurred (data cutoff, 7 April 2021) and from an extended data cutoff (19 August 2021) for primary and key secondary efficacy

end points, safety end points, and characterization of variants of concern.

The trial was conducted in accordance with the ethical principles derived from international guidelines, including the Declaration of Helsinki (7th revision, 2013), Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice Guidelines, and all applicable laws and regulations. The protocol and amendments were reviewed and approved by an institutional review board or ethics committee. All participants provided written informed consent.

Participants were aged ≥18 years with potential exposure within 8 days to a symptomatic or asymptomatic individual with laboratory-confirmed SARS-CoV-2 infection and who were at appreciable risk of imminently developing COVID-19 based on available risk assessment at time of enrollment, within a high SARS-CoV-2 exposure risk setting (Supplementary Material). Participants must not have had COVID-19 symptoms (Supplementary Table 1) within 10 days before dosing. Participants with previous laboratory-confirmed SARS-CoV-2 infection or seropositivity (based on rapid point-of-care test) at screening or receipt of COVID-19 vaccination were excluded. Full eligibility criteria are provided in the Supplementary Material. A nasopharyngeal swab was collected at screening for SARS-CoV-2 by central laboratory reverse-transcription polymerase chain reaction (RT-PCR) for future analysis.

Randomization and Masking

Participants were randomized 2:1 to a single 300-mg AZD7442 dose (one 1.5-mL injection of each mAb consecutively) or saline placebo (two 1.5-mL injections consecutively) intramuscularly on day 1 and monitored for safety for 1–4 hours post dosing. Participants were initially stratified into cohort 1 (aged ≥60 years living in LTCFs with occurrence of SARS-CoV-2 infection in another resident or staff member) or cohort 2 (aged ≥18 years exposed to SARS-CoV-2 within a prespecified high exposure risk setting; Supplementary Material). A protocol amendment (v6.0, 12 March 2021) removed caps for cohorts 1 and 2 not to exceed 80% of the total participants, as recruitment of participants from LTCFs was judged no longer feasible with the availability of COVID-19 vaccines.

Participants who received study intervention and became eligible for a COVID-19 vaccine could request to be unblinded (at any time) to consider COVID-19 vaccination and remain in the study (Supplementary Material).

Outcomes

The primary safety end point was safety and tolerability of a single intramuscular dose of AZD7442 vs placebo, assessed by adverse events (AEs), serious AEs (SAEs), medically attended AEs (MAAEs), and AEs of special interest (AESIs). The primary efficacy end point was first incidence of post-dose SARS-CoV-2
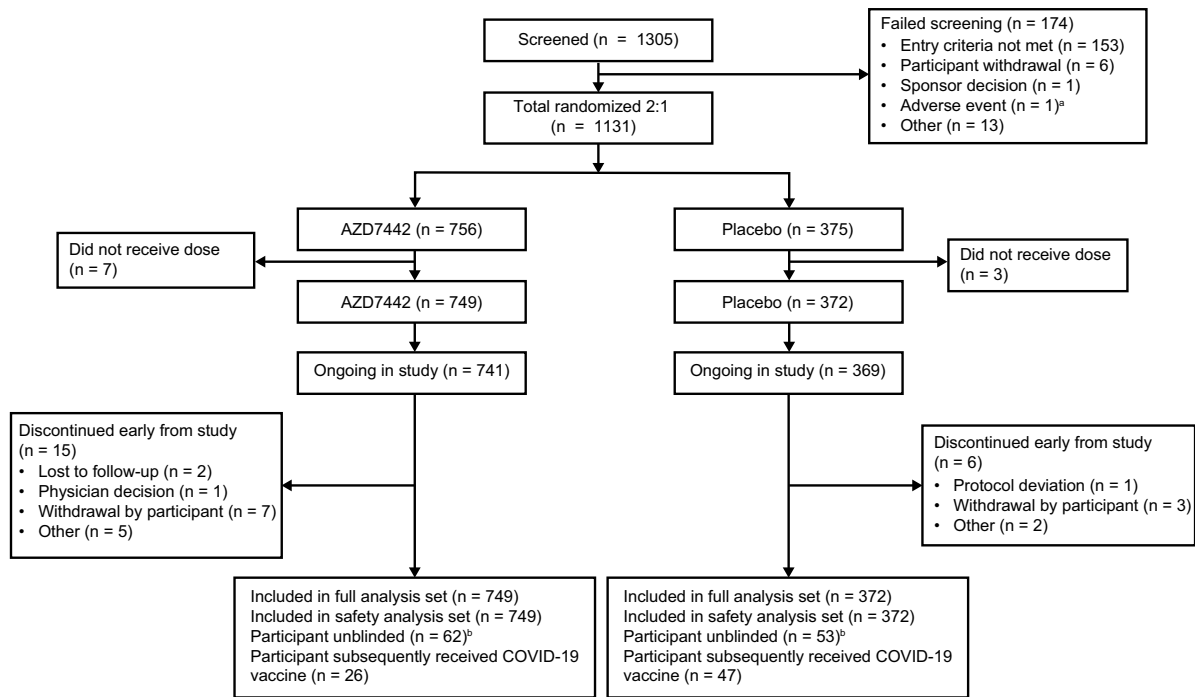
Figure 1. Participant disposition. [a]This potential participant experienced elevated blood pressure during screening and was not included in the study. [b]Participants who received study intervention and became eligible for a COVID-19 vaccine could request to be unblinded to consider vaccination for COVID-19 and remain in the study. For participants who were unblinded before the primary efficacy end point, data were collected and analyzed regardless. Abbreviations: AZD7442, tixagevimab/cilgavimab; COVID-19, coronavirus disease 2019.

RT-PCR–positive symptomatic illness (hereafter referred to as symptomatic COVID-19) occurring before day 183, assessed 30 days after the 25th event had occurred. The day 183 time point was selected to coincide with the expected duration of the effect of AZD7442, based on modeling analyses [17].

Further details of end points and the analysis methods are provided in the Supplementary Material.

Statistical Analyses

For analysis of the primary efficacy end point, a study population of approximately 1125 participants randomized in a 2:1 ratio, assuming a 4.5% attack rate with placebo and 75% true efficacy (equating to an attack rate of 1.1% with AZD7442), was estimated to provide approximately 90% power to demonstrate the lower bound of the 2-sided 95% confidence interval (CI) for efficacy to be >0. Based on these assumptions, a minimum of 25 cases was required to demonstrate efficacy.

The primary efficacy analysis was performed using a Poisson regression model with robust variance with log of follow-up time as an offset to estimate relative risk of symptomatic COVID-19 with AZD7442 vs placebo. Efficacy was calculated as relative risk reduction (RRR) for symptomatic COVID-19. Efficacy is presented with a 2-sided CI, with statistical significance achieved if the 95% CI lower bound was >0. To support the primary analysis, a Cox proportional hazard model was fitted to the data and Kaplan–Meier curves presented for active and control

groups. Deaths caused by COVID-19 and hospitalizations characterized as severe COVID-19 (Supplementary Table 2) were also considered within the definition of a primary efficacy event. Further information is detailed in the Supplementary Material.

The key secondary efficacy end point and the other secondary efficacy end points were analyzed following the same methodology as for the primary efficacy end point. Subgroup analyses are detailed in the Supplementary Material. Missing data were not imputed for the efficacy end points (Supplementary Material).

Data from participants who were unblinded to consider COVID-19 vaccination or vaccinated prior to the primary efficacy end point were included in the efficacy and safety analyses.

RESULTS

Between 2 December 2020 and 19 March 2021, 1305 participants were screened. Of these, 1131 participants had exposure to SARS-CoV-2 within 8 days and were randomized 2:1 to AZD7442 or placebo; 10 participants were not dosed, resulting in 749 participants receiving AZD7442 and 372 receiving placebo (Figure 1).

In the full analysis set, mean (standard deviation) age was 46 (16) years with 20% of participants aged ≥60 years and 99.4% in cohort 2 (Table 1). Most participants were SARS-CoV-2 RT-PCR–negative (n = 974, 87%) or had a missing RT-PCR status (n = 99, 9%) at baseline; 34 (4.5%) participants in the

Table 1. Participant Demographics and Baseline Clinical Characteristics: Full Analysis Set

Characteristic	AZD7442 (Tixagevimab/Cilgavimab) (n = 749)	Placebo (n = 372)	Total (N = 1121)
Cohort, n (%)			
1 (aged ≥60 y, living in long-term care facility)	5 (0.7)	2 (0.5)	7 (0.6)
2 (other adults aged ≥18 y, exposed to SARS-CoV-2 within prespecified high exposure risk settings)	744 (99.3)	370 (99.5)	1114 (99.4)
Age, mean (SD), y	46.6 (15.7)	46.0 (16.2)	46.4 (15.9)
Age group, n (%), y			
≥60	149 (19.9)	75 (20.2)	224 (20.0)
≥65	91 (12.1)	43 (11.6)	134 (12.0)
≥75	23 (3.1)	16 (4.3)	39 (3.5)
Female, n (%)	373 (49.8)	181 (48.7)	554 (49.4)
Ethnicity, n (%)			
Not Hispanic or Latino	299 (39.9)	159 (42.7)	458 (40.9)
Hispanic or Latino	435 (58.1)	210 (56.5)	645 (57.5)
Unknown/Not reported	15 (2.0)	3 (0.8)	18 (1.6)
Race, n (%)			
White	628 (83.8)	315 (84.7)	943 (84.1)
Black or African American	76 (10.1)	36 (9.7)	112 (10.0)
Asian	15 (2.0)	13 (3.5)	28 (2.5)
American Indian/Alaska Native	6 (0.8)	1 (0.3)	7 (0.6)
Native Hawaiian/Pacific Islander	2 (0.3)	1 (0.3)	3 (0.3)
Unknown/Not reported/Multiple	22 (2.9)	6 (1.6)	28 (2.5)
BMI, mean (SD), kg/m^2	29.7 (6.7)	29.9 (6.7)	29.7 (6.7)
SARS-CoV-2 reverse-transcription polymerase chain reaction status, n (%)			
Negative	646 (86.2)	328 (88.2)	974 (86.9)
Positive	34 (4.5)	14 (3.8)	48 (4.3)
Missing data	69 (9.2)	30 (8.1)	99 (8.8)
SARS-CoV-2 nucleocapsid antibodies serostatus at baseline, n (%)			
Negative	444 (59.3)	231 (62.1)	675 (60.2)
Positive	65 (8.7)	30 (8.1)	95 (8.5)
Missing data	240 (32.0)	111 (29.8)	351 (31.3)
At risk for severe coronavirus disease 2019, n (%)			
Any risk factor	492 (65.7)	244 (65.6)	736 (65.7)
Obesity (BMI ≥30 kg/m^2)	295 (39.4)	162 (43.5)	457 (40.8)
Hypertension	184 (24.6)	84 (22.6)	268 (23.9)
Smoking	144 (19.2)	71 (19.1)	215 (19.2)
Diabetes	90 (12.0)	38 (10.2)	128 (11.4)
Asthma	49 (6.5)	27 (7.3)	76 (6.8)
Cancer	24 (3.2)	10 (2.7)	34 (3.0)
Cardiovascular disease	19 (2.5)	14 (3.8)	33 (2.9)
Chronic kidney disease	14 (1.9)	7 (1.9)	21 (1.9)
Chronic obstructive pulmonary disease	7 (0.9)	11 (3.0)	18 (1.6)
Chronic liver disease	8 (1.1)	2 (0.5)	10 (0.9)
Immunosuppressive treatment	7 (0.9)	2 (0.5)	9 (0.8)
Sickle cell disease	1 (0.1)	0	1 (0.1)
Immunosuppressive disease	0	0	0

Data cutoff, 7 April 2021.

Abbreviations: BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

AZD7442 group and 14 (3.8%) in the placebo group were SARS-CoV-2 RT-PCR–positive. A small proportion in the AZD7442 and placebo groups (8.7% and 8.1%, respectively) were subsequently determined to be SARS-CoV-2–seropositive at baseline (based on central laboratory serum antinucleocapsid testing). Overall, 736 (66%) participants had ≥1 risk factor for severe COVID-19 (Table 1). Median (range) duration of follow-up at primary data cutoff was 49 (5–115) and 48 (20–113) days for AZD7442 and placebo, respectively. Median (range) duration of follow-up at extended data cutoff (19 August 2021) was 182 (5–249) and 178 (11–247) days for AZD7442 and placebo, respectively.

Table 2. Adverse Events at the Primary Data Cutoff: Safety Analysis Set

Participants With ≥1 Event, n (%)	AZD7442 (Tixagevimab/Cilgavimab) (n = 749)	Placebo (n = 372)	Total (N = 1121)
AE	162 (21.6)	111 (29.8)	273 (24.4)
Mild	103 (13.8)	74 (19.9)	177 (15.8)
Moderate	51 (6.8)	31 (8.3)	82 (7.3)
Severe	7 (0.9)	6 (1.6)	13 (1.2)
Potentially life-threatening	1 (0.1)[a]	0	1 (0.1)
SAE	5 (0.7)	3 (0.8)	8 (0.7)
Intervention-related SAE[b]	0	0	0
AE leading to study withdrawal	0	0	0
Medically attended AE	32 (4.3)	16 (4.3)	48 (4.3)
AE of special interest	4 (0.5)	5 (1.3)	9 (0.8)
Injection-site reaction[c]	4 (0.5)	4 (1.1)	8 (0.7)
Other	0	1 (0.3)	1 (0.1)
General pruritus	0	1 (0.3)	1 (0.1)
Intervention-related AE of special interest[b]	3 (0.4)	5 (1.3)	8 (0.7)
AE with outcome death	0	0	0

Data cutoff, 7 April 2021. AEs were defined as any AE that started or worsened in severity on or after the first dose of study intervention. AEs were coded using the *Medical Dictionary for Regulatory Activities*, version 24.0. Participants with >1 event within a preferred term were counted once for that preferred term. Percentages are based on the number of participants in the analysis set by study intervention group (N).

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a]Potentially life-threatening event reported as overdose, not considered related to study intervention.

[b]AEs were determined to be related to study intervention or study procedures by the investigators based on their judgment.

[c]Includes events of injection-site pain, injection-site pruritus, other injection-site reaction, and pruritus.

In the safety analysis, at the primary data cutoff, ≥ 1 AE was reported by 162 of 749 (21.6%) and 111 of 372 (29.8%) participants in the AZD7442 and placebo groups, respectively, with 95% reporting mild or moderate AEs (Table 2). The most common AEs included headache, fatigue, and cough (Supplementary Table 3). SAEs were reported by 5 (0.7%) and 3 (0.8%) participants in the AZD7442 and placebo groups, respectively; none were considered related to study intervention (Table 2, Supplementary Table 4). AESIs were reported by 4 (0.5%) and 5 (1.3%) participants in the AZD7442 and placebo groups, respectively, mostly injection site reactions (Table 2). No AEs led to study withdrawal or death.

Safety at the extended data cutoff was generally consistent with the primary data cutoff (Supplementary Table 5). There were 3 deaths: 2 (0.3%) participants in the AZD7442 group (metastatic lung cancer, cerebral ischemia) and 1 (0.3%) participant in the placebo group (unexplained death); none were considered related to study intervention.

In the efficacy analysis, at the primary data cutoff, symptomatic COVID-19 developed in 23 of 749 (3.1%) participants in the AZD7442 group vs 17 of 372 (4.6%) in the placebo group (Figure 2A). The treatment difference was not statistically significant (RRR, 33.3%; 95% CI, −25.9 to 64.7; P = .21; absolute risk reduction 1.50; 95% CI, −.76 to 4.32; P = .23). Time to first post-dose symptomatic COVID-19 before day 183 is shown in Figure 2A. Most (87.5%) events occurred within the expected post-exposure SARS-CoV-2 incubation period (11 days post-dose); all 23 events in the AZD7442 group (17 events in baseline SARS-CoV-2 RT-PCR–positive participants) and 12 events with placebo (70.6% of total events observed with placebo; 5 events in baseline SARS-CoV-2 RT-PCR–positive participants), with an additional 5 events occurring with placebo after day 11.

By the extended data cutoff, symptomatic COVID-19 developed in 27 of 749 (3.6%) participants in the AZD7442 group vs 23 of 372 (6.2%) in the placebo group (RRR, 43.2%; 95% CI, .1 to 67.7; nominal P = .049). Time to first post-dose symptomatic COVID-19 at the extended data cutoff is shown in Figure 2A.
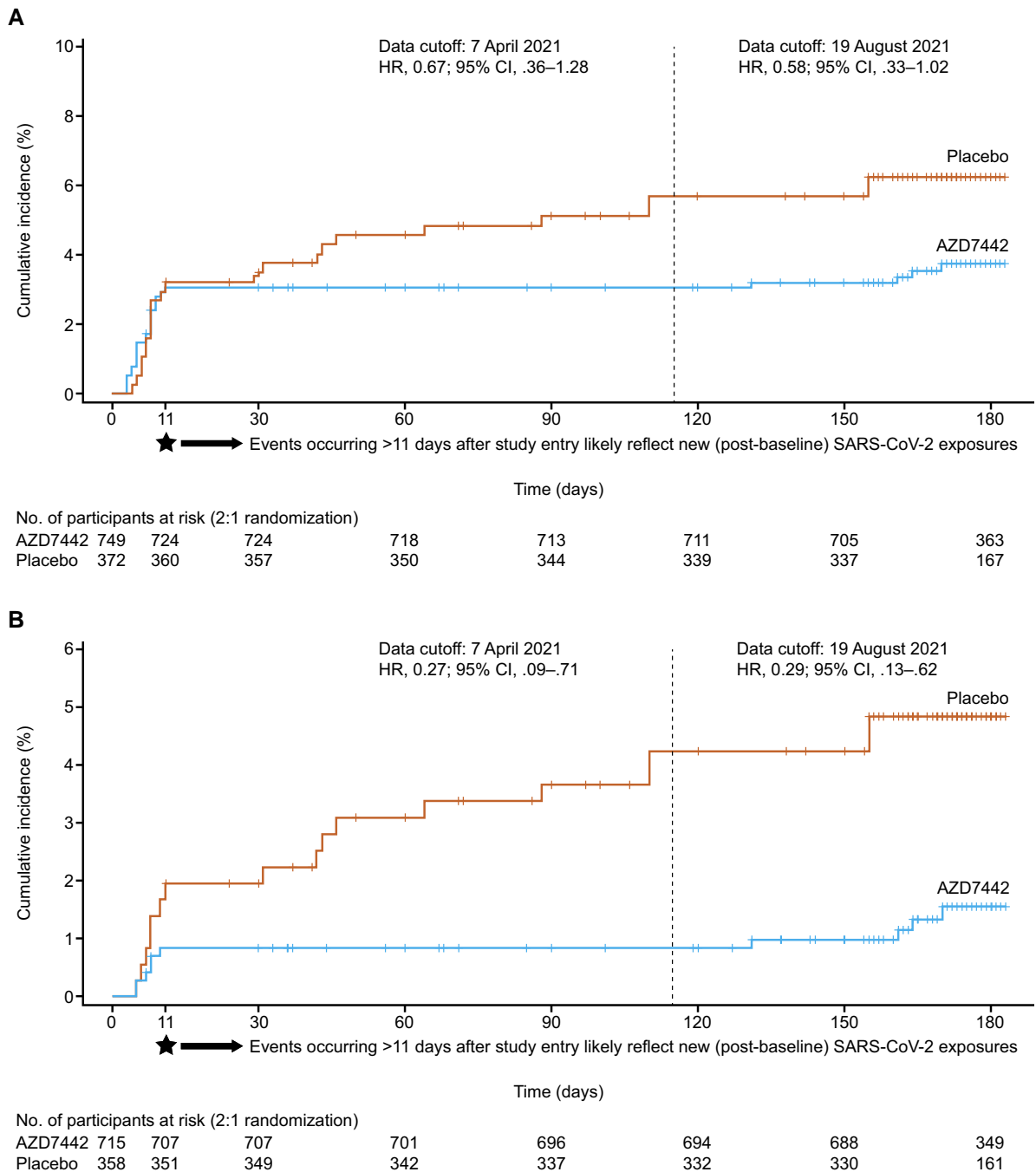
In predefined subgroup analyses among 1073 (96%) participants who were SARS-CoV-2 RT-PCR–negative or missing an RT-PCR result at baseline, symptomatic COVID-19 developed in 6 of 715 (0.8%) participants in the AZD7442 group vs 11 of 358 (3.1%) in the placebo group, resulting in an RRR of 73.2% (95% CI, 27.1 to 90.1; Figures 2B and 3) at primary data cutoff, with consistent results at the extended data cutoff (RRR, 71.5%; 95% CI, 37.5 to 87.0; Figure 2B). Findings for other subgroup analyses at primary data cutoff were generally consistent with the overall primary analysis population (Figure 3, Supplementary Figure 1).

For the key secondary end point at the primary data cutoff, severe or critical COVID-19 developed in 0 of 749 (0%) participants in the AZD7442 group and 1 of 372 (0.3%) in the placebo group (RRR not evaluable). No additional severe or critical events were reported during the extended follow-up.

Findings for the following secondary and exploratory end points are reported for the primary data cutoff only. As no deaths occurred by primary data cutoff, COVID-19–related death and all-cause mortality could not be analyzed. One (0.1%) and 2 (0.5%) participants in the AZD7442 and placebo groups, respectively, had COVID-19–related emergency department visits. There were no significant differences in post-dose seroconversion between groups, regardless of symptom status, suggesting that AZD7442 did not prevent asymptomatic SARS-CoV-2 infection (Supplementary Table 6).

SARS-CoV-2 sequencing data were available from 16 of 27 (59.2%) and 11 of 23 (47.8%) participants in the AZD7442 and placebo groups, respectively, who had symptomatic SARS-CoV-2 infection at extended follow-up. Sequencing data indicated that 12 participants were infected with the Alpha variant, and few cases (n = 3) of the Delta variant were identified (Supplementary Table 7).

In the pharmacokinetic analysis, AZD7442 reached and maintained high concentrations following dosing, as shown by geometric mean (± geometric standard deviation) serum concentrations of 18.7 (±2.0) μg/mL at day 8 and 24.9 (±1.5) μg/mL at day 58 (Supplementary Figure 2).
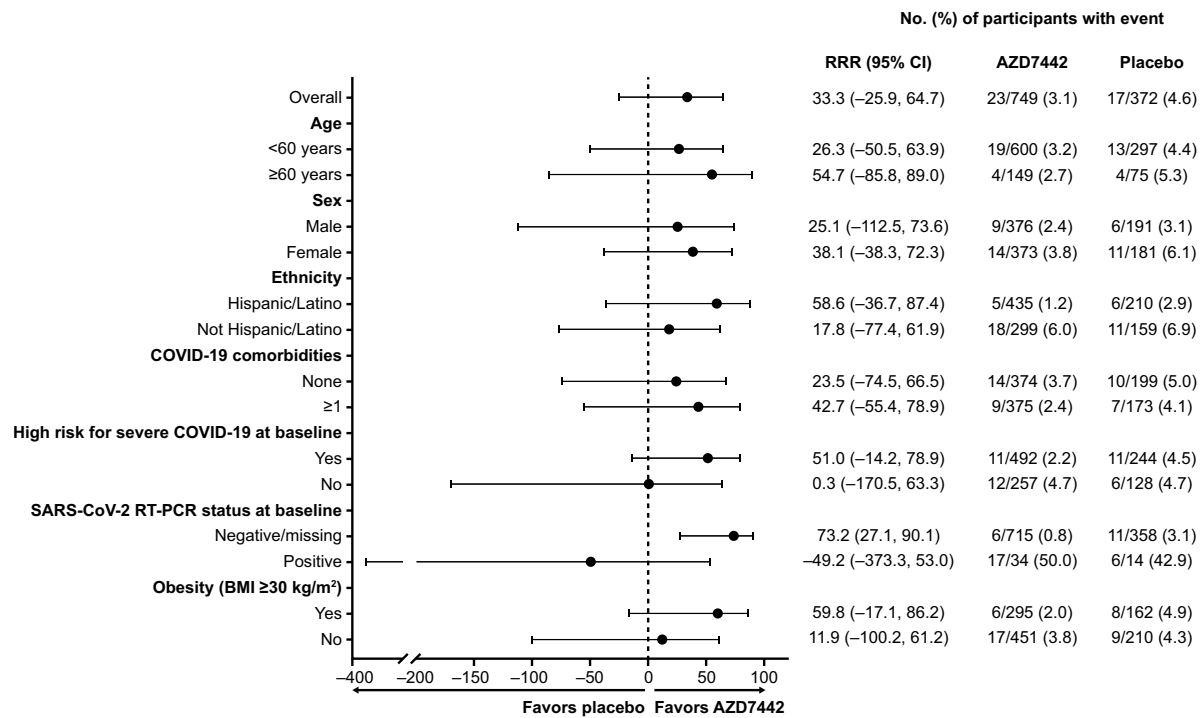
Figure 2. Time to first post-dose SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR)–positive symptomatic illness before day 183. *A,* The full analysis set. *B,* Predefined analysis of participants who were SARS-CoV-2 RT-PCR–negative or missing an RT-PCR result at baseline. + Indicates a censored observation. Dashed line represents the primary data cutoff. HR is from the proportional hazard model with the Efron method. The 95% CI for the HR was obtained by taking 95% profile likelihood CI of the HR from the proportional hazard model. Abbreviations: AZD7442, tixagevimab/cilgavimab; CI, confidence interval; HR, hazard ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DISCUSSION

STORM CHASER did not meet the primary efficacy end point of reducing symptomatic COVID-19 with post-exposure prophylaxis of AZD7442 vs placebo among the full study population. However, AZD7442 was effective in preventing symptomatic COVID-19 in participants who were SARS-CoV-2 RT-PCR–negative or missing an RT-PCR result at baseline, and results suggested a protective effect over 6 months, consistent with an equivalent population in the PROVENT pre-exposure prevention study [21]. AZD7442

No. (%) of participants with event

	RRR (95% CI)	AZD7442	Placebo
Overall	33.3 (−25.9, 64.7)	23/749 (3.1)	17/372 (4.6)
Age			
<60 years	26.3 (−50.5, 63.9)	19/600 (3.2)	13/297 (4.4)
≥60 years	54.7 (−85.8, 89.0)	4/149 (2.7)	4/75 (5.3)
Sex			
Male	25.1 (−112.5, 73.6)	9/376 (2.4)	6/191 (3.1)
Female	38.1 (−38.3, 72.3)	14/373 (3.8)	11/181 (6.1)
Ethnicity			
Hispanic/Latino	58.6 (−36.7, 87.4)	5/435 (1.2)	6/210 (2.9)
Not Hispanic/Latino	17.8 (−77.4, 61.9)	18/299 (6.0)	11/159 (6.9)
COVID-19 comorbidities			
None	23.5 (−74.5, 66.5)	14/374 (3.7)	10/199 (5.0)
≥1	42.7 (−55.4, 78.9)	9/375 (2.4)	7/173 (4.1)
High risk for severe COVID-19 at baseline			
Yes	51.0 (−14.2, 78.9)	11/492 (2.2)	11/244 (4.5)
No	0.3 (−170.5, 63.3)	12/257 (4.7)	6/128 (4.7)
SARS-CoV-2 RT-PCR status at baseline			
Negative/missing	73.2 (27.1, 90.1)	6/715 (0.8)	11/358 (3.1)
Positive	−49.2 (−373.3, 53.0)	17/34 (50.0)	6/14 (42.9)
Obesity (BMI ≥30 kg/m²)			
Yes	59.8 (−17.1, 86.2)	6/295 (2.0)	8/162 (4.9)
No	11.9 (−100.2, 61.2)	17/451 (3.8)	9/210 (4.3)

−400 −200 −150 −100 −50 0 50 100

Favors placebo Favors AZD7442

Figure 3. Key predefined subgroup analysis of incidence of first post-dose SARS-CoV-2 RT-PCR–positive symptomatic illness before day 183. Data cutoff, 7 April 2021. Estimates are based on Poisson regression with robust variance or exact Poisson regression or exact conditional method for Poisson. The model includes the log of the follow-up time as an offset and a covariate for study intervention (AZD7442 vs placebo). Estimated RRR >0 ([1 − relative risk with AZD7442 vs placebo] × 100%) provides evidence in favor of AZD7442. Further subgroup analyses are shown in Supplementary Figure 1. Abbreviations: AZD7442, tixagevimab/cilgavimab; BMI, body mass index; 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.

demonstrated a favorable safety profile and was well tolerated in STORM CHASER, consistent with other phase 3 studies, including those evaluating AZD7442 for treatment of mild to moderate COVID-19 (TACKLE) and severe COVID-19 (ACTIV-3) [21–23].

Although the impact of AZD7442 as post-exposure prophylaxis on development of severe COVID-19 (including hospitalization, respiratory failure, and death) could not be assessed in STORM CHASER due to the low number of events (1 case of severe disease in the placebo arm), the potential of AZD7442 to prevent development of severe COVID-19 was demonstrated in the phase 3 TACKLE trial, in which AZD7442 reduced the risk of developing severe COVID-19 or death vs placebo by 50.5%, 66.9%, and 88.0% among participants with mild-to-moderate COVID-19 who had been symptomatic for ≤7, ≤ 5, and ≤3 days, respectively [22]. These data also support the premise that treating earlier in the course of infection is more effective.

Eligible participants in STORM CHASER had SARS-CoV-2 exposure within 8 days of randomization, and time from SARS-CoV-2 exposure to AZD7442 administration likely impacted the primary efficacy results. At baseline, 4.5% and 3.8% of participants in the AZD7442 and placebo groups,

respectively, were already SARS-CoV-2 RT-PCR–positive. However, as the date of initial SARS-CoV-2 exposure was participant reported, time from SARS-CoV-2 exposure to dosing could not be objectively confirmed or further explored. The study included a highly exposed population, so it is possible that participants may have had continuous exposure following randomization and had not started incubating prior to dosing. Furthermore, some participants had already seroconverted at baseline, based on more sensitive central laboratory serology testing for which results were not immediately available. This may be suggestive of a later disease course, though we cannot rule out the possibility that participants had a previous infection, and this likely further impacted the efficacy analysis. Analyses of early post-exposure prophylaxis within 4 days of exposure with another SARS-CoV-2 neutralizing mAb combination found greater reductions in COVID-19 among participants who were RT-PCR–negative vs RT-PCR–positive at baseline (RRRs of 81.4% and 31.5%, respectively) [24, 25]. Comparison of these studies supports that earlier treatment is more effective in preventing symptomatic COVID-19.

While this study was primarily designed to assess AZD7442 against development of COVID-19 symptoms following a reported exposure event (ie, post-exposure), the design (which

assessed events up to day 183, capturing events after the expected 11-day incubation period) enabled an assessment of AZD7442 in pre-exposure prevention. Symptomatic COVID-19 events that occurred >11 days after study entry likely reflect new post-baseline exposures, and the reduction in these events with AZD7442 vs placebo over the 6-month follow-up supports a protective effect against new SARS-CoV-2 exposures owing to the extended half-life of AZD7442 [17], consistent with the results of the PROVENT study [21].

Participants could request to be unblinded to consider COVID-19 vaccination. Following unblinding, a greater proportion of participants in the placebo group than the AZD7442 group subsequently received COVID-19 vaccine (12.6% vs 3.5%, respectively). This imbalance may have biased the efficacy analysis in the assessment of pre-exposure prevention (ie, against events occurring later in the study). Therefore, the reported protective effect of AZD7442 against new SARS-CoV-2 exposures after the index exposure may be underestimated.

This study had several limitations. Efficacy results were likely affected by the period of up to 8 days allowed between exposure and randomization, which resulted in a large proportion of events in participants who were already SARS-CoV-2 RT-PCR–positive at baseline. There was a low number of symptomatic COVID-19 cases overall following index exposure, potentially due to the exclusion of the LTCFs cohort and subsequent enrollment of a younger, healthier population than was planned. Individuals living in LTCFs still remain an at-risk population in which further evaluation of post-exposure prophylaxis may be warranted, especially in the context of waning COVID-19 vaccine effectiveness, emergence of new variants, and continued SARS-CoV-2 transmission [26]. Individuals with prior receipt of a COVID-19 vaccination were not eligible to participate in STORM CHASER. However, AZD7442 has been shown to not interfere with COVID-19 vaccine immunogenicity [27], and initial evidence suggests that AZD7442 may augment pre-existing protection against SARS-CoV-2 infection in immunocompromised individuals who are fully vaccinated [28, 29]. Although efficacy of AZD7442 against Omicron could not be assessed in the present study, in vitro studies have demonstrated that AZD7442 retains neutralizing activity against the BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3, BA.4, and BA.5 Omicron subvariants, with resultant potency within the half maximal inhibitory concentration (IC_{50}) geometric mean concentration range of 4.0–806.0 ng/mL [18–20, 30–33]. Following AZD7442 administration, the resultant anti–SARS-CoV-2 neutralizing antibody titer in sera is higher than that of convalescent serum and is therefore expected to be clinically effective against these Omicron subvariants [17]. Importantly, AZD7442 retains potency against the BA.2 Omicron subvariant (IC_{50} of 10 ng/mL vs 4.0–9.8 ng/mL for ancestral strain vs BA.2, respectively) [20, 30], as well against BA.4/5 (IC_{50} 40–65 ng/mL) [31, 34]. Finally, this study used a 300-mg intramuscular dose of AZD7442. To provide optimal protection against emerging variants for vulnerable populations, a revised dosage regimen of 600 mg AZD7442 (300 mg each of tixagevimab and cilgavimab) every 6 months is now recommended for pre-exposure prophylaxis of COVID-19 [30].

CONCLUSIONS

AZD7442 300 mg intramuscular administration in participants with index exposure to SARS-CoV-2 within 8 days showed favorable safety but did not meet the primary efficacy end point of reduction in symptomatic COVID-19 cases. Findings among participants from high exposure risk environments who were SARS-CoV-2 RT-PCR–negative or missing an RT-PCR result at baseline support a role for AZD7442 in prevention of symptomatic COVID-19.

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