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MAJOR ARTICLE

Prevention of COVID-19 Following a Single Intramuscular Administration of Adintrevimab: Results From a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial (EVADE)

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Background. The prevention of coronavirus disease 2019 (COVID-19) in vulnerable populations is a global health priority. EVADE was a phase 2/3 multicenter, double-blind, randomized, placebo-controlled trial of adintrevimab, an extended–half-life monoclonal antibody, for postexposure (PEP) and pre-exposure prophylaxis (PrEP) of symptomatic COVID-19.

Methods. Eligible participants (vaccine-naive, aged ≥12 years) were randomized 1:1 to receive a single 300-mg intramuscular injection of adintrevimab or placebo. Primary efficacy end points were reverse transcription polymerase chain reaction (RT-PCR)–confirmed symptomatic COVID-19 through day 28 in the PEP cohort (RT-PCR-negative at baseline) and through month 3 in the PrEP cohort (RT-PCR-negative and seronegative at baseline) among participants randomized before emergence of the severe acute respiratory syndrome coronavirus 2 Omicron variant (November 30, 2021). Safety was assessed through 6 months.

Results. Between April 27, 2021, and January 11, 2022, 2582 participants were randomized. In the primary efficacy analysis, RT-PCR-confirmed symptomatic COVID-19 occurred in 3/175 (1.7%) vs 12/176 (6.8%) adintrevimab- and placebo-treated PEP participants, respectively (74.9% relative risk reduction [RRR]; standardized risk difference, −5.0%; 95% CI, −8.87% to −1.08%; $P = .0123$) and in 12/752 (1.6%) vs 40/728 (5.5%) adintrevimab- and placebo-treated PrEP participants, respectively (71.0% RRR; standardized risk difference, −3.9%; 95% CI, −5.75% to −2.01%; $P < .0001$). In a prespecified exploratory analysis of 428 PrEP participants randomized after the emergence of Omicron, adintrevimab reduced RT-PCR-confirmed symptomatic COVID-19 by 40.6% (standardized risk difference −8.4%; 95% CI, −15.35% to −1.46%; nominal $P = .0177$) vs placebo. Adintrevimab was well tolerated, with no serious drug-related adverse events reported.

Conclusions. A single intramuscular injection of adintrevimab provided prophylactic efficacy against COVID-19 due to susceptible variants without safety concerns.

Clinical trial registration. NCT04859517.

Keywords. COVID-19; SARS-CoV-2; adintrevimab; monoclonal antibody; prevention.

Despite the widespread availability of vaccines and treatment options, coronavirus disease 2019 (COVID-19) continues to place a high burden on patients, society, and health care systems [1–3], with >671 million cases and >6.8 million deaths reported globally as of February 7, 2023 [4]. In the United States, COVID-19 was the third leading cause of death during the pandemic, surpassed only by cancer and heart disease [5]. Furthermore, up to 30% of individuals have been reported to suffer persistent long-term symptoms after COVID-19 [6, 7], with substantial loss in quality of life, reduced job productivity, and high medical expenditures [1, 8].

Vaccination is the primary approach to COVID-19 prevention [9]. However, individuals who are not fully vaccinated or who respond inadequately to vaccines (eg, immunocompromised) are at high risk of infection and severe disease [10]. Moreover, waning of immune protection and emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with enhanced transmissibility and/or relative resistance to neutralization by vaccine-induced antibody responses have contributed to the need for additional prevention approaches [11, 12].

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The unique properties of neutralizing monoclonal antibodies (mAbs) address several vaccine limitations. Vaccines require weeks, and in some cases multiple doses, to induce a protective immune response [13]. In contrast, protection with mAbs is more immediate, making them well-suited agents for postexposure prophylaxis (PEP); mAbs can provide a reliable level of neutralizing titers regardless of host immune status [14], and the duration of protection against newly emergent SARS-CoV-2 variants can be predicted based on pharmacokinetic modeling [15, 16].

Adintrevimab (ADG20) is a fully human immunoglobulin G1 mAb derived from a survivor of the 2003 SARS-CoV epidemic and engineered for improved potency and broad neutralization against SARS-CoV-2 and other SARS-like coronaviruses with pandemic potential [17, 18]. The Fc region of adintrevimab contains an LA modification (428L/434A) designed to extend half-life [16]. Adintrevimab binds to an epitope in the receptor-binding domain of the spike glycoprotein of SARS-CoV-2 that partially overlaps the human angiotensin–converting enzyme 2 binding site and is conserved across most of the sarbecovirus subgenus [17].

Adintrevimab has demonstrated prophylactic efficacy in animal models [19] and broad and potent in vitro neutralizing activity against most SARS-CoV-2 variants, including Alpha, Beta, Gamma, and Delta [20, 21]. However, adintrevimab has reduced in vitro neutralizing activity against Omicron BA.1 and BA.1.1 and lacks activity against more recent Omicron sublineages [22, 23].

Based on quantitative pharmacology/population-based pharmacokinetic modeling and preliminary pharmacokinetic data from a phase 1 study [24–26], a single 300-mg intramuscular adintrevimab injection was selected for evaluation in the EVADE trial for the prevention of symptomatic COVID-19 in 2 cohorts, PEP and pre-exposure prophylaxis (PrEP). Given limited neutralization of Omicron BA.1 by adintrevimab, enrollment in EVADE was suspended in January 2022, and primary analyses were limited to participants randomized before emergence of the Omicron variant.

Here, we report the efficacy and safety outcomes from the EVADE trial.

METHODS

Trial Design and Participants

EVADE was a multicenter, double-blind, placebo-controlled, randomized phase 2/3 trial (NCT04859517). Eighty-eight sites randomized participants in 8 countries (Supplementary Data, p3).

Eligible participants were adults (≥18 years) and adolescents (12 to <18 years) whose circumstances placed them at risk of acquiring SARS-CoV-2 infection. The PEP cohort comprised participants with reported recent exposure to an individual testing positive for SARS-CoV-2 (index case); randomization occurred within 5 days from both exposure to and sample collection from the index case (based on a verbal report from the participant). The PrEP cohort had no known recent exposure but did have occupational, housing, recreational, or social circumstances that increased their risk of exposure. Participants whose advanced age (≥55 years) or health status placed them at risk for developing severe COVID-19 or COVID-19 complications, such as chronic cardiopulmonary disease, diabetes, obesity, or an immune-compromised state, were included. A detailed list of risk factors for severe COVID-19 can be found in the Supplementary Data (p12).

Participants were eligible if they tested negative for past SARS-CoV-2 infection via serology (including by a rapid test) and for current SARS-CoV-2 infection via reverse transcription polymerase chain reaction (RT-PCR) testing at screening. PEP participants could be randomized without RT-PCR and serology results if the results were not available by screening day 5. Participants were excluded if they had received any prior COVID-19 vaccine, convalescent plasma, or mAb, including in a clinical trial. A full list of inclusion/exclusion criteria can be found in the Supplementary Data (p8).

The first participant was randomized April 27, 2021; enrollment was paused January 11, 2022, due to the emergence and subsequent global spread of Omicron BA.1/BA.1.1 variants. Pharmacokinetic/pharmacodynamic analyses incorporating adintrevimab's reduced in vitro activity against BA.1/BA.1.1 variants suggested that the 300-mg intramuscular dose might not provide durable and clinically meaningful protection against disease caused by this variant. The statistical analysis plan and protocol were amended before unblinding (Supplementary Data, p6) to evaluate the primary efficacy end point in the subset of participants randomized before the emergence of the Omicron variant (randomized on/before November 30, 2021; referred to as the pre-Omicron set). In addition, the primary efficacy end point for the PrEP cohort was revised to analyze COVID-19 events through month 3 compared with the originally planned month 6 to allow assessment of efficacy against the Delta variant before the widespread emergence of Omicron. Efficacy and safety outcomes are reported through the data cutoff of July 25, 2022, when participants had completed 6 months of safety follow-up. The trial was terminated on October 26, 2022, as continued safety follow-up was not expected to yield additional safety information.

Patient Consent

Written informed consent was obtained from all participants. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable regulations. The protocol was reviewed and approved by an

institutional review board or ethics committee in each country. In the United States, Advarra (Columbia, MD, USA) approved the study for all sites. The full protocol is available as Supplementary Data.

Randomization and Blinding

Participants were randomized 1:1 to receive a single 300-mg intramuscular injection of adintrevimab or placebo. Randomization was blinded; participants were stratified using a centralized interactive response technology (IRT) system according to geographic region (United States, Central/Eastern Europe, and rest of world) and age/risk for developing severe/critical COVID-19 (age 12 to <55 years and low risk, age 12 to <55 and high risk, and age ≥55 years).

Limited personnel (including site pharmacist, designated clinical research associates, and clinical trial manager for drug supply monitoring) were not blinded to study drug assignment. A preliminary analysis was performed by an independent clinical research organization in March 2022 to assess the primary efficacy end point. Specific sponsor personnel were unblinded subsequently to prepare potential interactions with regulatory agencies and inform further study and program plans. All study participants, investigators, other site staff, and sponsor personnel (or designees) working directly with the clinical sites were blinded to the study drug assignment until database lock.

Analysis Populations and End Points

The full analysis set (FAS) included all randomized participants regardless of receipt of study drug. The pre-Omicron analysis set included FAS participants randomized on or before November 30, 2021. The post-Omicron analysis set included the remaining FAS participants randomized between December 1, 2021, and January 11, 2022. Whole-genome sequencing (WGS; Eurofins Viracor BioPharma, Lenexa, KS, USA) was used to confirm the SARS-CoV-2 variant from nasopharyngeal swabs or saliva samples, as previously described [16].

The primary efficacy end point in the PEP cohort was the proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through day 28 or December 15, 2021, whichever was earlier, in participants randomized before the emergence of Omicron and without current SARS-CoV-2 infection (RT-PCR-negative) at baseline regardless of serostatus (pre-Omicron modified FAS-1 [mFAS-1]).

The primary efficacy end point in the PrEP cohort was the proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through month 3 or December 15, 2021, whichever was earlier, in participants randomized before the emergence of Omicron and without prior or current SARS-CoV-2 infection (RT-PCR-negative and seronegative as confirmed by central testing) at baseline (pre-Omicron mFAS).

Prespecified secondary efficacy end points included time from randomization to first RT-PCR-confirmed symptomatic COVID-19 and assessment of maximum COVID-19 severity through 28 days postdiagnosis. A prespecified exploratory analysis evaluated the proportion of participants with RT-PCR-confirmed symptomatic COVID-19 through day 28 in the PEP cohort and through month 3 in the PrEP cohort in the post-Omicron mFAS-1/mFAS, respectively.

A post hoc analysis evaluated the incidence of RT-PCR-confirmed symptomatic COVID-19 through 6 months in a subset of PrEP participants and PEP participants who were considered PrEP-like (PEP participants who did not have an event in the first 28 days) who were randomized on or before June 15, 2021, and followed for at least 180 days through December 15, 2021.

Safety was assessed in all participants who received study drug, including treatment-emergent adverse events (TEAEs), serious adverse events (AEs), vital signs, and clinical laboratory assessments. Solicited injection-site reactions (ISRs) and hypersensitivity reactions were recorded through day 4.

Statistical Analysis

Primary end points were analyzed using the methodology for determining a standardized estimator for a binary outcome and associated CIs as detailed by Ge et al. [27], and the analysis was adjusted for predefined prognostic factors, including treatment, randomization stratification factors (geographic region, age/risk of severe COVID-19), and baseline serology status when applicable. Time from randomization to first RT-PCR-confirmed symptomatic COVID-19 was analyzed using stratified log-rank testing by Kaplan-Meier methodology and a stratified Cox proportional-hazards model to estimate the hazard ratio adjusted for the predefined prognostic factors. Exploratory and safety end points were analyzed using descriptive statistics.

The statistical analysis plan is available as Supplementary Data. Additional details on study methodology including sample size calculations and handling of missing data and intercurrent events are provided in the Supplementary Data (p15).

RESULTS

Participants

A total of 5951 people were screened; 2582 participants were randomized (Figure 1). In the PEP cohort, 487 participants were randomized to receive adintrevimab (n = 245) or placebo (n = 242); 5 participants in the adintrevimab group and 1 in the placebo group did not receive study drug and were excluded from the safety population (n = 481). The primary efficacy analysis set (pre-Omicron mFAS-1) included 175 participants in the adintrevimab group and 176 in the placebo group. In

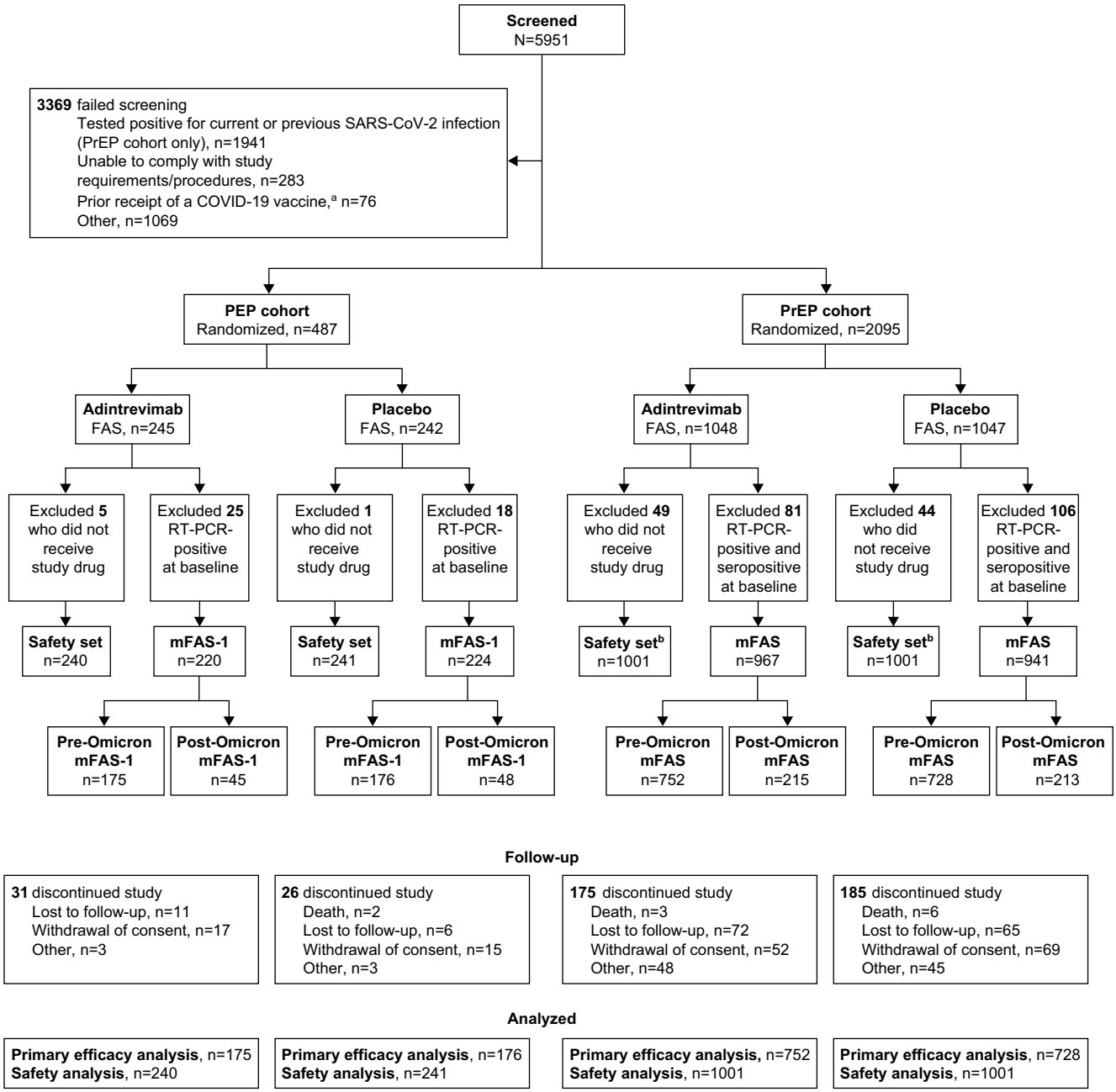


Figure 1. Disposition and analysis populations. [a]Included COVID-19 vaccine received in a clinical trial setting. Immune-compromised participants who had completed a COVID-19 vaccine series may have been enrolled if other criteria were met. [b]Two participants randomized to placebo were treated with adintrevimab and are therefore included in the adintrevimab group for safety analysis. Abbreviations: COVID-19, coronavirus disease 2019; mFAS, modified full analysis set RT-PCR-negative and seronegative at baseline; mFAS-1, modified full analysis set RT-PCR-negative at baseline regardless of serostatus; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

the PrEP cohort, 2095 participants were randomized to receive adintrevimab (n = 1048) or placebo (n = 1047); 49 participants in the adintrevimab group and 44 in the placebo group did not receive study drug and were excluded from the safety population (n = 2002). The primary efficacy analysis set (pre-Omicron mFAS) included 752 participants in the adintrevimab group and 728 in the placebo group.

In the primary efficacy populations, baseline characteristics were similar across treatment groups within each cohort (Table 1). The median age of participants was 47 years; 10 participants (<1%) were aged 12 to <18 years, ~31% were aged ≥55 years, and 52% were female. Participants were primarily White (79%) and enrolled in the United States (83%); 30% were Hispanic or Latinx, and 16% were Black or African

Table 1. Demographic and Baseline Characteristics of the Primary Efficacy Populations by Cohort and Treatment

Pre-Omicron Analysis Set	PEP Cohort (mFAS-1): RT-PCR-Negative Regardless of Serostatus at Baseline			PrEP Cohort (mFAS): RT-PCR-Negative and Seronegative at Baseline		
Characteristic	Adintrevimab (n = 175)	Placebo (n = 176)	Overall (n = 351)	Adintrevimab (n = 752)	Placebo (n = 728)	Overall (n = 1480)
Median age (range), y	47 (17–86)	47 (18–86)	47 (17–86)	46 (13–84)	47 (12–87)	47 (12–87)
12 to <18	1 (0.6)	0	1 (0.3)	7 (0.9)	2 (0.3)	9 (0.6)
18 to <55	118 (67.4)	121 (68.8)	239 (68.1)	519 (69.0)	496 (68.1)	1015 (68.6)
55 to <75	50 (28.6)	50 (28.4)	100 (28.5)	213 (28.3)	215 (29.5)	428 (28.9)
≥75	6 (3.4)	5 (2.8)	11 (3.1)	13 (1.7)	15 (2.1)	28 (1.9)
Sex						
Male	78 (44.6)	89 (50.6)	167 (47.6)	356 (47.3)	352 (48.4)	708 (47.8)
Female	97 (55.4)	87 (49.4)	184 (52.4)	396 (52.7)	376 (51.6)	772 (52.2)
Race						
Native American or Alaska Native	0	0	0	2 (0.3)	7 (1.0)	9 (0.6)
Asian	0	0	0	9 (1.2)	5 (0.7)	14 (0.9)
Black or African American	19 (10.9)	19 (10.8)	38 (10.8)	122 (16.2)	131 (18.0)	253 (17.1)
Native Hawaiian or other Pacific Islander	0	0	0	4 (0.5)	5 (0.7)	9 (0.6)
White	156 (89.1)	156 (88.6)	312 (88.9)	586 (77.9)	553 (76.0)	1139 (77.0)
Other	0	0	0	18 (2.4)	17 (2.3)	35 (2.4)
Multiple	0	1 (0.6)	1 (0.3)	11 (1.5)	10 (1.4)	21 (1.4)
Ethnicity						
Hispanic or Latinx	102 (58.3)	98 (55.7)	200 (57.0)	166 (22.1)	178 (24.5)	344 (23.2)
Not Hispanic or Latinx	73 (41.7)	78 (44.3)	151 (43.0)	552 (73.4)	521 (71.6)	1073 (72.5)
Not reported	0	0	0	26 (3.5)	27 (3.7)	53 (3.6)
Unknown	0	0	0	8 (1.1)	2 (0.3)	10 (0.7)
Geographic region						
United States	126 (72.0)	124 (70.5)	250 (71.2)	647 (86.0)	621 (85.3)	1268 (85.7)
Central/Eastern Europe	49 (28.0)	52 (29.5)	101 (28.8)	103 (13.7)	104 (14.3)	207 (14.0)
Rest of world[a]	0	0	0	2 (0.3)	3 (0.4)	5 (0.3)
BMI						
No.	175	176	351	751	723	1474
Mean (SD), kg/m^2	28.1 (5.9)	27.6 (5.5)	27.9 (5.7)	29.2 (7.4)	29.7 (7.6)	29.5 (7.5)
SARS-CoV-2 antibody serology status[b]						
Negative	72 (41.1)	77 (43.8)	149 (42.5)	732 (97.3)	712 (97.8)	1444 (97.6)
Positive	97 (55.4)	95 (54.0)	192 (54.7)	0	0	0
Missing	6 (3.4)	4 (2.3)	10 (2.8)	20 (2.7)	16 (2.2)	36 (2.4)
SARS-CoV-2 RT-PCR status[c]						
Detected	0	0	0	0	0	0
Not detected	172 (98.3)	173 (98.3)	345 (98.3)	693 (92.2)	684 (94.0)	1377 (93.0)
Missing	3 (1.7)	3 (1.7)	6 (1.7)	59 (7.8)	44 (6.0)	103 (7.0)
Age/risk of severe/critical COVID-19 (IRT)						
≥12 to <55 y and low risk	61 (34.9)	63 (35.8)	124 (35.3)	232 (30.9)	227 (31.2)	459 (31.0)
≥12 to <55 y and high risk	58 (33.1)	57 (32.4)	115 (32.8)	289 (38.4)	273 (37.5)	562 (38.0)
≥55 y	56 (32.0)	56 (31.8)	112 (31.9)	231 (30.7)	228 (31.3)	459 (31.0)
Severe COVID-19 risk factors[d]						
Adults (age ≥18), No. with data	174	176	350	745	726	1471
Obesity	41 (23.6)	39 (22.2)	80 (22.9)	160 (21.5)	176 (24.2)	336 (22.8)
Diabetes (type 1 or 2)	17 (9.8)	9 (5.1)	26 (7.4)	59 (7.9)	67 (9.2)	126 (8.6)
Chronic kidney disease	2 (1.1)	0	2 (0.6)	10 (1.3)	6 (0.8)	16 (1.1)
Chronic lung disease	6 (3.4)	5 (2.8)	11 (3.1)	44 (5.9)	41 (5.6)	85 (5.8)
Cardiac disease	33 (19.0)	26 (14.8)	59 (16.9)	124 (16.6)	145 (20.0)	269 (18.3)
Sickle cell disease or thalassemia	0	0	0	3 (0.4)	0	3 (0.2)
Solid organ or blood stem cell transplant recipients	1 (0.6)	0	1 (0.3)	0	0	0
Other immunodeficiency[e]	2 (1.1)	3 (1.7)	5 (1.4)	11 (1.5)	10 (1.4)	21 (1.4)
Down syndrome	1 (0.6)	0	1 (0.3)	0	0	0
Stroke or cerebrovascular disease	2 (1.1)	0	2 (0.6)	5 (0.7)	9 (1.2)	14 (1.0)
Substance use disorder	0	2 (1.1)	2 (0.6)	48 (6.4)	65 (9.0)	113 (7.7)

Table 1. Continued

Pre-Omicron Analysis Set	PEP Cohort (mFAS-1): RT-PCR-Negative Regardless of Serostatus at Baseline			PrEP Cohort (mFAS): RT-PCR-Negative and Seronegative at Baseline		
Characteristic	Adintrevimab (n = 175)	Placebo (n = 176)	Overall (n = 351)	Adintrevimab (n = 752)	Placebo (n = 728)	Overall (n = 1480)
Adolescents (age <18 y), No.	1	0	1	7	2	9
Obesity	0	0	0	1 (14.3)	0	1 (11.1)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; eCRF, electronic case report form; IRT, interactive response technology; mFAS, modified full analysis set RT-PCR-negative and seronegative at baseline; mFAS-1, modified full analysis set RT-PCR-negative at baseline regardless of serostatus; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Rest of world = Argentina.

[b]Baseline SARS-CoV-2 antibody serology status was assessed by central laboratory testing and considered positive if baseline serology antibody to either N or S protein was positive; if both serology test results were missing, the overall status was missing; otherwise, overall status was considered negative. For analysis set definition, participants with missing baseline serology status were imputed to be seronegative if their postbaseline serology test was negative.

[c]Baseline SARS-CoV-2 RT-PCR status was considered detected if baseline nasopharyngeal or nasal swab results were positive; if both baseline nasopharyngeal and nasal swab results were missing, the overall status was missing; otherwise, overall status was considered not detected. For analysis set definition, participants with missing baseline RT-PCR status were imputed to be RT-PCR-negative if their postbaseline serology test was negative. The collection of nasal swab tests was not required per the protocol for the PrEP cohort.

[d]Participants may have >1 risk factor; participants with missing age were considered adults. The severe COVID-19 disease risk factors were medically adjudicated by the sponsor based on medical history and prior/concomitant medications recorded in the eCRF.

[e]Due to underlying illness or immunosuppressant medication.

American. Based on age and comorbidities, >60% of participants in both cohorts were at high risk for severe disease. In the PEP cohort, 55% of participants were seropositive for SARS-CoV-2 at baseline, highlighting that many participants who were negative on rapid serology at screening were later found to be positive on central laboratory serology testing. Baseline characteristics of the FAS are in Supplementary Table 1.

Efficacy, Pre-Omicron Analysis

PEP Cohort

In the PEP mFAS-1 cohort, RT-PCR-confirmed symptomatic COVID-19 through day 28 occurred in 3/175 (1.7%) participants in the adintrevimab group and 12/176 (6.8%) in the placebo group (Table 2), representing a 74.9% relative risk reduction (RRR) favoring adintrevimab, with a standardized risk difference of −5.0% (95% CI, −8.87% to −1.08%; $P = .0123$). WGS data for the causative SARS-CoV-2 variant were available for 10/15 (66.7%) of these participants; all cases of COVID-19 were due to Delta variants (Supplementary Table 2).

The prophylactic efficacy of adintrevimab was observed across key predefined subgroups, including participants at high risk for severe COVID-19 based on age and/or presence of comorbidities (Figure 2*A*). Prespecified analysis of time to first RT-PCR-confirmed symptomatic COVID-19 (Figure 3*A*) verified the findings of the primary analysis, with a statistically significant reduction in risk of symptomatic COVID-19 with adintrevimab vs placebo (hazard ratio [HR], 0.22; 95% CI, 0.06 to 0.76; log-rank $P = .0077$). Adintrevimab was also associated with a reduction in maximum severity of disease. Fewer severe/critical COVID-19 cases within 28 days postdiagnosis were seen among participants who received adintrevimab vs placebo (0 adintrevimab, 3 placebo) (Supplementary Table 3).

PrEP Cohort

In the PrEP mFAS, RT-PCR-confirmed symptomatic COVID-19 through month 3 occurred in 12/752 (1.6%) participants in the adintrevimab group and 40/728 (5.5%) in the placebo group (Table 2), representing a 71.0% RRR favoring adintrevimab, with a standardized risk difference of −3.9% (95% CI, −5.75% to −2.01%; $P < .0001$). WGS data for the causative SARS-CoV-2 variant were available for 40/52 (77.0%) of these participants; all cases of COVID-19 were due to Delta variants, except for 1 case due to the Alpha variant (Supplementary Table 2).

Similar to the PEP cohort, prophylactic efficacy of adintrevimab was observed across key predefined subgroups (Figure 2*B*). Prespecified analysis of time to first RT-PCR-confirmed symptomatic COVID-19 (Figure 3*B*) revealed a statistically significant reduction in risk of symptomatic COVID-19 with adintrevimab vs placebo (HR, 0.27; 95% CI, 0.14 to 0.49; log-rank $P < .0001$). Fewer severe/critical COVID-19 cases within 28 days postdiagnosis were seen among participants who received adintrevimab vs placebo (1 adintrevimab, 7 placebo) (Supplementary Table 3).

To evaluate 6-month prophylactic efficacy, we conducted an exploratory post hoc analysis of pooled data from a subset of participants (in both cohorts, PrEP and PEP) followed for at least 180 days. In this subset (adintrevimab, n = 60; placebo, n = 56), adintrevimab reduced the relative risk of RT-PCR-positive symptomatic COVID-19 through month 6 by 84.4% (standardized risk difference, −8.8%; 95% CI, −17.3% to −0.4%; nominal $P = .0410$) vs placebo (Supplementary Table 4).

Table 2. Primary End Point: Proportion of Participants With RT-PCR-Confirmed Symptomatic COVID-19 in the PEP Cohort (Pre-Omicron mFAS-1) and PrEP Cohort (Pre-Omicron mFAS)

PEP Cohort (Pre-Omicron mFAS-1)		
Events	Adintrevimab (n = 175)	Placebo (n = 176)
RT-PCR-confirmed symptomatic COVID-19 through d 28, No. (%)	3 (1.7)	12 (6.8)
Symptomatic COVID-19	3 (1.7)	12 (6.8)
COVID-19-related hospitalization	0	2 (1.1)
All-cause death	0	0
Treatment difference		
Relative risk reduction, %	74.9	
Standardized risk difference[a] (95% CI), %	−5.0 (−8.87 to −1.08)	
2-sided *P* value	.0123	
PrEP cohort (Pre-Omicron mFAS)		
Events	Adintrevimab (n = 752)	Placebo (n = 728)
RT-PCR-confirmed symptomatic COVID-19 through mo 3, No. (%)	12 (1.6)	40 (5.5)
Symptomatic COVID-19	12 (1.6)	39 (5.4)
COVID-19-related hospitalization	1 (0.1)	6 (0.8)
All-cause death	0	1 (0.1)
Treatment difference		
Relative risk reduction, %	71.0	
Standardized risk difference[b] (95% CI), %	−3.9 (−5.75 to −2.01)	
2-sided *P* value	<.0001	

Abbreviations: COVID-19, coronavirus disease 2019; mFAS, modified full analysis set RT-PCR-negative and seronegative at baseline; mFAS-1, modified full analysis set RT-PCR-negative at baseline regardless of serostatus; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; RT-PCR, reverse transcription polymerase chain reaction.

[a]The population-level standardized estimator was derived from a logistic regression model fitted to the binary outcome predicted by treatment, baseline serostatus (considered "positive" if missing), and randomization stratification factors (geography and age/risk category).

[b]The population-level standardized estimator was derived from a logistic regression model fitted to the binary outcome predicted by treatment and randomization stratification factors (geography and age/risk category).

Efficacy, Post-Omicron Analysis

PEP Cohort

In a prespecified exploratory analysis of the post-Omicron mFAS-1, RT-PCR-confirmed symptomatic COVID-19 through day 28 occurred in 4/45 (8.9%) and 2/48 (4.2%) participants in the adintrevimab and placebo groups, respectively (Supplementary Table 5). WGS data were available for 5/6 (83.3%) of these participants; all cases of COVID-19 were due to Omicron variants (Supplementary Table 2).

PrEP Cohort

In a prespecified exploratory analysis of the post-Omicron mFAS cohort, RT-PCR-confirmed symptomatic COVID-19 through month 3 occurred in 27/215 (12.6%) and 45/213 (21.1%) participants in the adintrevimab and placebo groups, respectively (RRR, 40.6%) (Supplementary Table 5). WGS data were available for 62/72 (86.1%) of these participants; all cases of COVID-19 were due to Omicron variants, except for 2 due to Delta variants (Supplementary Table 2).

Safety

The analysis of safety was pooled for both cohorts and included 2483 participants, of whom 1241 received adintrevimab and 1242 placebo. Two participants randomized to the placebo group received adintrevimab and were included in the adintrevimab group for safety analysis (Figure 1). The median duration of follow-up was 39 weeks. Incidence of TEAEs was similar between treatment groups (adintrevimab, 35.5%; placebo, 33.3%) (Table 3). The most frequently reported TEAEs were injection site pain (adintrevimab 6.9%, placebo 7.2%), influenza-like illness (adintrevimab 4.4%, placebo 3.5%), and upper respiratory tract infection (adintrevimab 3.2%, placebo 2.5%). Overall, solicited ISRs (injection site pain, tenderness, erythema/redness, and/or swelling) were reported in 8.2% of participants in each group. Two hypersensitivity reactions were reported, 1 mild urticaria in the adintrevimab group and 1 mild rash and pruritus in the placebo group.

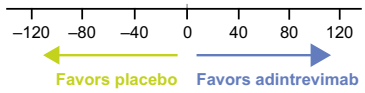
Serious TEAEs were reported in 43 (3.5%) participants in the adintrevimab group and 47 (3.8%) in the placebo group (Table 3). Three TEAEs led to death in the adintrevimab group, and 8 TEAEs led to death in the placebo group. No serious TEAEs or deaths were considered related to study drug (Supplementary Table 6). No safety concerns were identified for adintrevimab based on clinical laboratory or vital sign abnormalities.

DISCUSSION

The results of the EVADE trial demonstrated that a single 300-mg intramuscular injection of adintrevimab provided a

A **PEP Cohort**

Subgroup According to Baseline Characteristics	Adintrevimab, n/N Participants With Event	Placebo, n/N Participants With Event	Standardized Relative Risk Reduction (95% CI)
All	3/175 (1.7)	12/176 (6.8)	74.1% (13.13 to 92.26)
Sex			
Male	0/78 (0)	6/89 (6.7)	
Female	3/97 (3.1)	6/87 (6.9)	55.8% (–71.35 to 88.61)
Geographic region			
United States	0/126 (0)	2/124 (1.6)	
Central and Eastern Europe	3/49 (6.1)	10/52 (19.2)	67.5% (–10.43 to 90.46)
Age/risk of severe/critical COVID-19[a] (IRT)			
≥12 to <55 years and low risk	3/61 (4.9)	5/63 (7.9)	48.1% (–104.56 to 86.83)
≥12 to <55 years and high risk	0/58 (0)	5/57 (8.8)	
≥55 years	0/56 (0)	2/56 (3.6)	
Derived high risk of severe/critical COVID-19[b]			
Yes	0/98 (0)	4/93 (4.3)	
No	3/77 (3.9)	8/83 (9.6)	58.4% (–47.86 to 88.28)



B **PrEP Cohort**

Subgroup According to Baseline Characteristics	Adintrevimab, n/N Participants With Event	Placebo, n/N Participants With Event	Standardized Relative Risk Reduction (95% CI)
All	12/752 (1.6)	40/728 (5.5)	70.8% (44.83 to 84.52)
Sex			
Male	2/356 (0.6)	23/352 (6.5)	91.4% (63.83 to 97.96)
Female	10/396 (2.5)	17/376 (4.5)	45.1% (–18.10 to 74.52)
Geographic region			
United States	10/647 (1.5)	27/621 (4.3)	64.7% (27.74 to 82.80)
Central and Eastern Europe	2/103 (1.9)	13/104 (12.5)	84.5% (33.11 to 96.41)
Rest of world	0/2 (0)	0/3 (0)	
Age/risk of severe/critical COVID-19[a] (IRT)			
≥12 to <55 years and low risk	4/232 (1.7)	17/227 (7.5)	77.2% (33.46 to 92.21)
≥12 to <55 years and high risk	5/289 (1.7)	11/273 (4.0)	58.0% (–19.23 to 85.21)
≥55 years	3/231 (1.3)	12/228 (5.3)	74.1% (9.03 to 92.63)
Derived high risk of severe/critical COVID-19[b]			
Yes	7/436 (1.6)	21/461 (4.6)	64.8% (17.99 to 84.88)
No	5/316 (1.6)	19/267 (7.1)	77.8% (41.28 to 91.58)

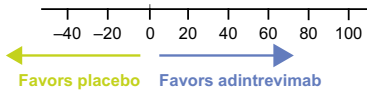


Figure 2. Relative risk reduction in the incidence of RT-PCR-confirmed symptomatic COVID-19 with adintrevimab vs placebo in the (*A*) PEP cohort through day 28 (pre-Omicron mFAS-1) and (*B*) PrEP cohort through month 3 (pre-Omicron mFAS), by key predefined subgroups. Subgroup categories with 100% RRR in favor of adintrevimab (no events in the adintrevimab group) are not represented graphically. [a]Age/risk stratification factors were recorded through the IRT. [b]Risk of severe/critical COVID-19 was derived from individual values recorded in the eCRF, such as age, medical history, and prior/concomitant medications. High risk of severe COVID-19 was defined as age ≥55 years or age ≥12 to <55 years and derived high risk based on medical history and prior/concomitant medications, which met the definition for high risk, as adjudicated by the sponsor. Abbreviations: COVID-19, coronavirus disease 2019; eCRF, electronic case report form; IRT, interactive response technology; mFAS, modified full analysis set RT-PCR-negative and seronegative at baseline; mFAS-1, modified full analysis set RT-PCR-negative at baseline regardless of serostatus; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; RRR, relative risk reduction; RT-PCR, reverse transcription polymerase chain reaction.

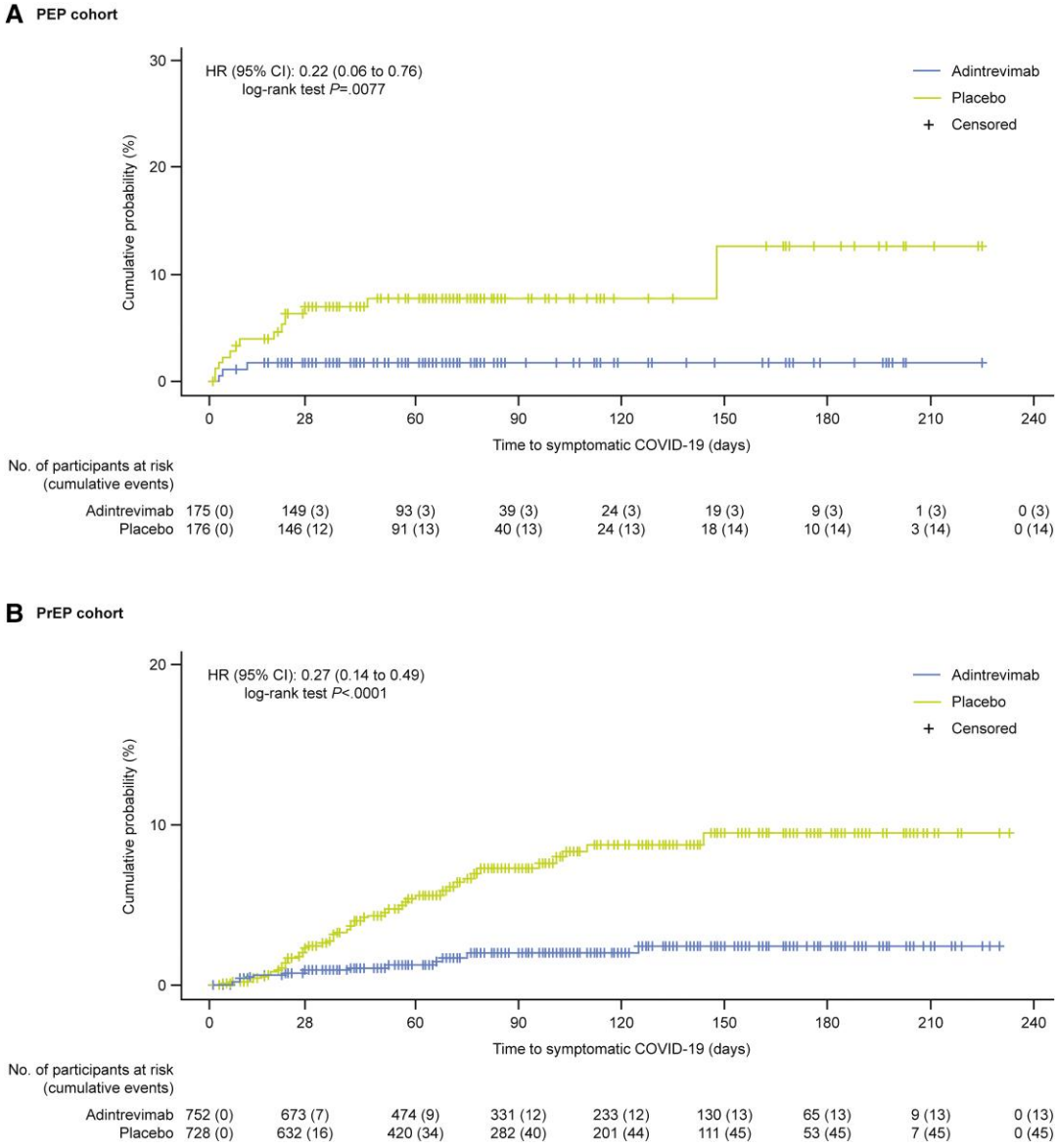


Figure 3. Time to first RT-PCR-confirmed symptomatic COVID-19 through December 15, 2021, in the (*A*) PEP cohort (pre-Omicron mFAS-1) and (*B*) PrEP cohort (pre-Omicron mFAS). Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; mFAS, modified full analysis set RT-PCR-negative and seronegative at baseline; mFAS-1, modified full analysis set RT-PCR-negative at baseline regardless of serostatus; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; RT-PCR, reverse transcription polymerase chain reaction.

statistically significant ($P < .05$) and clinically meaningful reduction in risk of RT-PCR-confirmed symptomatic COVID-19 compared with placebo among participants randomized before the emergence of Omicron, without safety concerns. These findings were consistent across 2 prevention cohorts, pre- and postexposure prophylaxis. Participants included in the primary efficacy analyses were primarily exposed to the Delta variant, which has been associated with higher rates of transmission and more severe disease, including hospitalization and/or death, compared with earlier variants [28, 29].

In the subgroup analysis, a favorable prophylactic effect of adintrevimab was observed in both the PEP and PrEP cohorts for participants aged >55 years and those with high risk for progression to severe COVID-19 because of comorbidities. Adintrevimab was also associated with reduction in severity of disease through day 28 postdiagnosis in those who developed RT-PCR-confirmed symptomatic COVID-19 compared with placebo. These results align with those reported for other mAbs as COVID-19 prevention strategies, including tixagevimab-cilgavimab [30] and casirivimab-imdevimab [31–33]. To date, adintrevimab is the only mAb to demonstrate

Table 3. Summary of Adverse Events (Safety Analysis Set, PEP, and PrEP Cohorts Combined)

Adverse Event Category, No. (%)	Adintrevimab (n = 1241)	Placebo (n = 1242)
Any TEAE	441 (35.5)	413 (33.3)
Unsolicited TEAE	378 (30.5)	351 (28.3)
Solicited TEAE (ISRs)[a]	102 (8.2)	102 (8.2)
Mild	84 (6.8)	79 (6.4)
Moderate	15 (1.2)	17 (1.4)
Severe	2 (0.2)	3 (0.2)
Missing grade of severity	1 (0.1)	3 (0.2)
Hypersensitivity reaction (by day 4)[b]	1 (0.1)	1 (0.1)
Most common TEAE (≥1% of participants)		
Injection site pain[a]	86 (6.9)	89 (7.2)
Influenza-like illness	55 (4.4)	44 (3.5)
Upper respiratory tract infection[c]	40 (3.2)	31 (2.5)
Headache	21 (1.7)	16 (1.3)
Nasopharyngitis	19 (1.5)	17 (1.4)
Sinusitis	18 (1.5)	13 (1.0)
Hypertension	17 (1.4)	21 (1.7)
Respiratory tract infection viral	16 (1.3)	14 (1.1)
Injection site swelling[a]	15 (1.2)	7 (0.6)
Injection site erythema[a]	15 (1.2)	18 (1.4)
Back pain	15 (1.2)	13 (1.0)
Urinary tract infection	14 (1.1)	9 (0.7)
Fatigue	14 (1.1)	8 (0.6)
Cough	12 (1.0)	5 (0.4)
Diarrhea	12 (1.0)	9 (0.7)
Viral rhinitis	7 (0.6)	12 (1.0)
COVID-19 pneumonia	2 (0.2)	12 (1.0)
Any grade ≥3 TEAE	48 (3.9)	51 (4.1)
Any serious TEAE	43 (3.5)	47 (3.8)
Any TEAE leading to death	3 (0.2)	8 (0.6)
Any study drug–related TEAE[d]	114 (9.2)	108 (8.7)
Any study drug–related serious TEAE[d]	0	0
Any study drug–related TEAE leading to death	0	0

Adverse events were coded using *Medical Dictionary for Regulatory Activities,* version 24.0.

Abbreviations: COVID-19, coronavirus disease 2019; ISR, injection site reaction; PEP, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; TEAE, treatment-emergent adverse event.

[a]ISRs included injection site pain, tenderness, erythema/redness, and swelling. All solicited TEAEs (ISRs) were assumed to be related to study drug.

[b]Hypersensitivity reactions through day 4 were determined by medical adjudication based on the narrow and broad terms of the Standardized *Medical Dictionary for Regulatory Activities* queries hypersensitivity, anaphylactic reaction, and angioedema.

[c]Cases of COVID-19 were not captured as AEs unless meeting serious criteria.

[d]A missing relationship to study drug was imputed as "related."

efficacy in phase 3 studies for PEP, PrEP, *and* treatment of COVID-19 [34].

Adintrevimab was well tolerated, with no unexpected safety concerns identified. As expected with intramuscular administration, solicited ISRs were reported in ~8% of participants in both groups. No drug-related serious AEs were reported, and no laboratory or vital sign trends were identified to indicate adintrevimab safety risks.

The efficacy assessment period of the study spanned the emergence and global spread of 2 SARS-CoV-2 variants, Delta and Omicron BA.1/BA1.1, against which adintrevimab exhibited marked differences (>100-fold) in neutralization potency. This provided a unique opportunity to assess the relationship between antibody potencies (ie, neutralization titers) of a low intramuscular dose of adintrevimab against different variants and assess clinical protection against symptomatic disease in a population lacking preexisting immunity to SARS-CoV-2 (the PrEP cohort). Pharmacokinetic/pharmacodynamic modeling showed that adintrevimab provided ~40% protection against symptomatic COVID-19 through month 3 in SARS-CoV-2-naive adults at serum-neutralizing titers on the order of 1:30 independent of variant, and consistent with the level of protection observed with vaccines that demonstrate 50% protection at a similar threshold antibody level [35]. The observed prophylactic efficacy of adintrevimab against Omicron BA.1/BA.1.1 in EVADE (41% through month 3) (Supplementary Table 5) and estimated serum-neutralizing titers against Omicron BA.1/BA.1.1 in the order of ~1:30 of the 300-mg intramuscular dose are highly consistent with pharmacokinetic/pharmacodynamic modeling and vaccine data [16]. These data support the validity of pharmacokinetic/pharmacodynamic modeling of serum-neutralizing titer thresholds as a correlate of protection against SARS-CoV-2 and provide insight for evaluation of dose and duration of protection when variants and potency change.

Strengths of the study include a high proportion of participants considered at high risk of severe COVID-19 because of advanced age or comorbidities and representation of diverse populations disproportionately impacted by the COVID-19 pandemic (eg, Black and Hispanic/Latinx populations) in pre- and postexposure settings.

A limitation was that the study was stopped early because of the emergence of Omicron, against which adintrevimab showed reduced in vitro activity, thus impacting the ability to evaluate longer-term protection of adintrevimab against COVID-19. Because the study was conducted only during the Delta and Omicron surges, efficacy results may not be generalizable to other variants. Similar to other phase 3 trials of mAbs for COVID-19 prevention [30], the study design for EVADE required enrollment of vaccine-naive participants, leading to low enrollment of some important subgroups with potential to benefit from mAb prophylaxis (eg, immune-compromised patients) and precluding the ability to evaluate efficacy in this population. Real-world evidence collected postauthorization for other SARS-CoV-2 mAbs highlights both the potential benefits of mAb prophylaxis for the immune compromised [36–39] and the need for additional data in this population [40].

CONCLUSIONS

In EVADE, a single intramuscular injection of adintrevimab was a well-tolerated and effective option for the prevention

of symptomatic COVID-19 due to susceptible variants of SARS-CoV-2. These data support continued development of mAbs for prevention of COVID-19, particularly for vulnerable populations that may not be protected through vaccination. Adintrevimab has demonstrated efficacy and safety in global phase 3 clinical trials for both the prevention and treatment of COVID-19 [34]. These data may have the potential to support accelerated development of future mAbs engineered from adintrevimab or utilizing the adintrevimab antibody scaffold, including VYD222. VYD222 was engineered from adintrevimab, has demonstrated in vitro neutralizing activity against currently circulating variants of concern, including XBB.1.5 [41], and is in phase 1 of clinical development (NCT05791318).

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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