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Subcutaneous REGEN-COV Antibody Combination in Early SARS-CoV-2 Infection

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ABSTRACT

Background: Casirivimab and imdevimab administered together (REGEN-COV™) markedly reduces the risk of hospitalization or death in high-risk, symptomatic individuals with COVID-19. Here, we report phase 3 results of early treatment of asymptomatic, SARS-CoV-2–positive adults and adolescents with subcutaneous REGEN-COV.

Methods: Individuals ≥12 years of age were eligible if identified within 96 hours of a household contact being diagnosed as SARS-CoV-2-positive; 314 were randomized 1:1 to receive subcutaneous REGEN-COV 1200mg or placebo. The primary endpoint was the proportion of infected participants without evidence of prior immunity (i.e., SARS-CoV-2-RT-qPCR–positive/seronegative) who subsequently developed symptomatic Covid-19 during a 28-day efficacy assessment period.

Results: Subcutaneous REGEN-COV 1200mg significantly prevented progression from asymptomatic to symptomatic disease compared with placebo (31.5% relative risk reduction; 29/100 [29.0%] vs. 44/104 [42.3%], respectively; P=0.0380). REGEN-COV also reduced the overall population burden of high viral load weeks (39.7% reduction vs. placebo; 48 vs. 82 total weeks; P=0.0010) and of symptomatic weeks (45.3% reduction vs. placebo; 89.6 vs. 170.3 total weeks; P=0.0273), the latter corresponding to an approximately 5.6-day reduction per symptomatic participant. Six placebo-treated participants had a Covid-19-related hospitalization or ER visit versus none for those receiving REGEN-COV. The proportion of participants receiving placebo who had ≥1

treatment-emergent adverse events was 48.1% compared to 33.5% for those receiving REGEN-COV, including Covid-19-related (39.7% vs. 25.8%, respectively) or non-Covid-19-related (16.0% vs. 11.0%, respectively) events.

Conclusions: Subcutaneous REGEN-COV 1200mg prevented progression from asymptomatic to symptomatic infection, reduced the duration of high viral load and symptoms, and was well tolerated.

(ClinicalTrials.gov number, NCT04452318.)

INTRODUCTION

SARS-CoV-2, a betacoronavirus first identified in China at the end of 2019, is the cause of Covid-19 and the current global pandemic that has infected over 140 million and resulted in the deaths of over 3 million persons to date.[1,2] Compared with other betacoronavirus infections, the incubation period of SARS-CoV-2 infection (i.e., time before symptoms occur) has features that complicate the control of virus transmission: the period is highly variable (range 2–14 days) and it is often characterized by high viral loads and viral shedding.[3-8] Once symptomatic, acute Covid-19 can persist for several weeks, with progression to severe disease, including hospitalization or death in up to 20% of individuals.[9] In addition, current data suggest that at least one-third of all SARS-CoV-2 infections have an asymptomatic course,[10-13] with high levels of viral shedding,[5,7,8] potentially driving the ongoing spread of SARS-CoV-2.[10,14-16] Easy-to-administer antiviral treatments that reduce SARS-CoV-2 burden early in the pre-symptomatic phase or in asymptomatic individuals could reduce the incidence of moderate and severe Covid-19 and blunt ongoing transmission.

REGEN-COV consists of two neutralizing monoclonal antibodies, casirivimab and imdevimab, that bind distinct, non-overlapping epitopes on the SARS-CoV-2 spike protein receptor binding domain and block virus entry.[17] The two-antibody combination reduces the risk of emergence of treatment-induced SARS-CoV-2 variants and retains neutralization potency in vitro against already-circulating variants of concern or interest (VOC/VOIs), including B.1.1.7, B.1.351, P.1, and B.1.427/429.[18-20] REGEN-COV administered intravenously has proven effective in treating Covid-19 outpatients,

reducing the risk of Covid-19–related hospitalization or all-cause death, rapidly resolving symptoms, and reducing viral load.[21,22]

In conducting a phase 3 randomized controlled trial to prevent SARS-CoV-2 infection in household contacts of an infected index case, we identified asymptomatic individuals in the same household who were already SARS-CoV-2-RT-qPCR–positive at the time of randomization. Here, we describe the results of early treatment of these individuals with subcutaneous REGEN-COV 1200mg.

METHODS

Trial Design

This randomized, double-blind, placebo-controlled, two-part phase 3 trial assessed the efficacy and safety of REGEN-COV in (Part A) preventing SARS-CoV-2 infection among uninfected household contacts of infected individuals and in (Part B) treating recently infected asymptomatic patients in the same households (ClinicalTrials.gov number, NCT04452318). The trial was conducted at 112 sites in the United States, Romania, and Moldova and was managed jointly by Regeneron, the Covid-19 Prevention Network (CoVPN), and the National Institute of Allergy and Infectious Diseases (NIAID).

Nasopharyngeal and serum samples were collected at the screening/baseline visit for central lab RT-qPCR testing and serum antibody testing. RT-qPCR was used to determine whether the patient had an ongoing SARS-CoV-2 infection, while baseline serology testing for serum anti-SARS-CoV-2 antibodies (anti-spike [S1] IgA, anti-spike [S1] IgG, and anti-nucleocapsid IgG) was used to determine a prior history of infection or an ongoing infection in which an endogenous antibody immune response had already occurred (i.e., seropositive; as opposed to seronegative). Part A included those who at baseline were RT-qPCR–negative and Part B included those who at baseline were RT-qPCR–positive (**Figure S1**). The patient populations for Part A and B were mutually exclusive and analyzed separately with different hierarchies and separate alpha allocation. Here we describe the results for Part B; results for Part A are described in a separate report.

Study participants were randomized (1:1) to receive REGEN-COV or placebo and stratified by SARS-CoV-2 local diagnostic results and age (see **Supplementary Appendix**). The trial consists of a 1-day screening/baseline period, a 28-day efficacy assessment period (EAP), and a 7-month follow-up period (**Figure S1**). The **Protocol** is available upon request.

Trial Oversight

The trial was conducted in accordance with the principles of the Declaration of Helsinki, GCP/ICH-E-9 guidelines, and all local and international regulatory standards. All participants provided written informed consent. Additional details are provided in the **Supplementary Appendix**.

Study Participants

The study included adults (≥18 years of age) and adolescents (≥12 to <18 years of age) who were household contacts of the first known household member with SARS-CoV-2 infection (index case) and who were SARS-CoV-2–positive by RT-qPCR and asymptomatic (having no active respiratory or non-respiratory symptoms consistent with Covid-19). Randomization occurred ≤96 hours of collection of the index case's positive SARS-CoV-2 test sample. The full list of inclusion/exclusion criteria are provided in the **Supplementary Appendix**.

Intervention and Assessments

At baseline (day 1), participants received a single dose of REGEN-COV 1200mg or placebo via subcutaneous (SC) injection.

Signs and symptoms of Covid-19 were collected by weekly investigator-led interviews. At each visit/contact, the investigator interviewed the participant about adverse events they were experiencing or may have experienced since the last visit/contact. If the participant developed signs and/or symptoms, this data was collected weekly until resolved.

Serial NP swabs were collected at baseline, prior to study drug administration, and weekly during the EAP and/or the follow-up period to determine SARS-CoV-2 viral load by RT-qPCR until participants tested negative on two consecutive swabs.

Details on the intervention, assessments, and analytical methods are provided in the **Protocol** or **Supplementary Appendix** or have been previously described.[22]

Endpoints

The primary efficacy endpoint was the proportion of participants who subsequently developed signs and symptoms of Covid-19 within 14 days of a positive RT-qPCR at baseline or during the efficacy assessment period. A broad definition (broad term) of what constituted symptomatic Covid-19 was used for the primary analysis; alternative

definitions (strict-term and CDC) were used for other analyses (see **Supplementary Appendix**).

The key secondary efficacy endpoints were the number of weeks (in the overall population) of symptomatic SARS-CoV-2 infection (broad-term) and the number of weeks of high viral load (>4 $\log_{10}$ copies/mL) in nasopharyngeal samples over 28 days. The full lists of secondary efficacy and exploratory endpoints and methods of calculation are provided in the **Statistical Analysis Plan** or **Supplementary Appendix**.

Safety endpoints included the collection of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and adverse events of special interest (AESIs) defined as grade ≥3 injection site reactions or hypersensitivity reactions.

Statistical Analysis

The statistical analysis plan for the presented analysis was finalized prior to database lock and treatment unblinding. The primary analysis population used for efficacy analyses was the seronegative modified full analysis set (seronegative mFAS-B): all randomized participants who were asymptomatic, confirmed positive for SARS-CoV-2 by central lab RT-qPCR, and negative for SARS-CoV-2 antibodies at baseline (i.e., part B in this two-part trial). All efficacy endpoints are reported through the 28-day EAP. The safety analysis set for part B (SAF-B) included all participants who received study drug (active or placebo). Efficacy and safety endpoints are reported for participants randomized through January 28, 2021 until the data cut-off date of March 11, 2021.

The sample size calculation assumed that approximately 200 seronegative participants would be enrolled and 50% of placebo participants would develop symptoms; this would provide >90% power to detect a relative risk of 0.5 at a two-sided alpha level of 0.05.

Hierarchical testing was employed for the primary and key secondary endpoints to control for type 1 error based on a two-sided alpha of 0.05. Participants with Covid-19 symptoms who were missing central lab RT-qPCR test results were considered as having a symptomatic infection if any symptoms occurred within 14 days of a positive SARS-CoV-2 local test.

Additional statistical and pharmacokinetic analysis methods are described in more detail in the **Statistical Analysis Plan** or **Supplementary Appendix**.

RESULTS

Trial Population

Between July 13, 2020 and January 28, 2021, a total of 314 household contacts were confirmed SARS-CoV-2 RT-qPCR–positive (PCR-positive) at baseline based on nasopharyngeal RT-qPCR; 156 study participants received placebo and 155 received REGEN-COV 1200mg SC; 3 randomized participants did not receive any study drug.

In order to best understand the earliest possible treatment effects of REGEN-COV, we limited the primary and key secondary analyses to asymptomatic individuals with no prior evidence of immunity, i.e., seronegative for antibodies against SARS-CoV-2. Of the 314 PCR-positive participants randomized, 207 (66%) were seronegative, 84 were seropositive (27%), and 23 (7%) were undetermined (**Figure S2**). Three seronegative participants were excluded from efficacy analyses as they were determined post-randomization to be symptomatic at baseline.

Demographics and baseline characteristics were well balanced across treatment arms (**Table 1**). For the primary analysis population, mean age was 40.9 years, 45% were male, 5.3% identified as Black or African American, and 35% identified as Hispanic or Latino. Nearly one-third of seronegative participants had ≥1 risk factor for severe Covid-19, including 13% who were obese (BMI ≥35 kg/m^2), 10% who were ≥65 years of age, and 8% who had diabetes. Similar demographics and characteristics were observed for participants who were seropositive at baseline (**Table S1**).

Prevention of Symptomatic Infection

In PCR-positive/seronegative asymptomatic participants, REGEN-COV 1200mg SC treatment significantly reduced the risk of developing a symptomatic infection compared with placebo (31.5% relative risk reduction; 29/100 [29.0%] vs. 44/104 [42.3%]; odds ratio 0.54 [95% CI, 0.30 to 0.97]; P=0.0380) (**Table 2; Figure 1A**). When symptom onset began 3 days or longer after treatment (day 4 to end of EAP), there was a 76.4% risk reduction in symptomatic infections with REGEN-COV vs. placebo (**Table S2**). Findings were similar when utilizing the study-defined broad-term or strict-term definitions of Covid-19 signs and symptoms or the CDC definition (**Table S3**).

There was a 45.3% reduction in the aggregated total number of weeks with symptoms (in the overall population) with REGEN-COV versus placebo: 89.6 vs. 170.3 weeks or 895.7 vs. 1,637.4 weeks per 1000 participants (P=0.0273; **Table 2; Figure 1B**). This corresponded to a 5.6-day reduction in the mean duration of symptoms per symptomatic participant with REGEN-COV (21.7 days) vs. placebo (27.3 days; **Table 2; Figure 1C**).

Virologic Efficacy

There was a more rapid decline in viral load in REGEN-COV 1200mg SC-treated participants as compared to those treated with placebo, with an adjusted mean difference in viral load of -1.5 $\log_{10}$ copies/mL in favor of the antibody combination at Day 8 (**Figure 2A; Figure S3; Table S4**).

The number of weeks of high viral load (>4 $\log_{10}$ copies/mL) was significantly reduced with REGEN-COV vs. placebo, with a 39.7% reduction in aggregated total number of weeks (in the overall population) (48 vs. 82 weeks or 489.8 vs. 811.9 weeks per 1000 participants; P=0.0010; **Table 2**). This corresponded to an approximately 2-day reduction per participant in days with high viral load from 5.7 days with placebo to 3.4 days with REGEN-COV (**Table 2; Figure 2B-2C**). Compared with placebo, REGEN-COV reduced peak viral load by approximately 1–2 $\log_{10}$ copies/mL both in participants who became symptomatic and in those who remained asymptomatic throughout the efficacy assessment period (**Figure 2D; Table S4**).

Prevention of Severe Disease

REGEN-COV 1200mg SC reduced the proportion of participants who had a Covid-19–related hospitalization or ER visit vs. placebo (0/100 vs. 6/104, respectively) (**Table S5**). Of the 6 participants in the placebo group, 3 went to the ER, 1 was hospitalized, and 2 went to the ER and were subsequently hospitalized. In contrast, no participants receiving REGEN-COV had ER visits or hospitalizations.

Efficacy in Participants by Baseline Serology Status

Although the primary analysis population focused on participants without evidence of prior infection (seronegative), analyses conducted in all participants (seronegative, seropositive, and undetermined) and in those who were seropositive demonstrated similar findings. In all participants and in the seropositive population, REGEN-COV reduced the risk of developing symptomatic infection vs. placebo by 35.4% and 33.9%,

respectively (**Table S6**). Similarly, in all participants, REGEN-COV reduced the duration of symptoms in those who became symptomatic, reduced the duration of weeks of detectable viral load and high viral load, and reduced peak viral load, with similar numerical trends in the seropositive-only population in most analyses (**Table S7-S10**).

Natural History

We compared the outcome of participants in the placebo group who had no evidence of immunity to SARS-CoV-2 (i.e., seronegative) and determined they were at higher risk of developing a symptomatic infection (44/104 [42.3%]) than those with evidence of immunity (i.e., seropositive; 5/38 [13.2%]) (**Table S6**). Seronegative participants had higher baseline nasopharyngeal viral loads (**Figure S4**) and higher maximum nasopharyngeal viral loads during the efficacy assessment period compared with those who were seropositive (median 5.1 vs. 2.6 $\log_{10}$ copies/mL, respectively; **Table S9**); the average duration of detectable viral RNA per participant was also longer (1.9 vs. 1.2 weeks, respectively). Viral load declined more slowly in the placebo group over the first 7 days than what has been observed in the treatment of symptomatic outpatients, consistent with presentation of these individuals early in the course of infection (**Figure S3**).[22]

Safety

REGEN-COV was generally well tolerated. A comparatively lower proportion of participants in the REGEN-COV group experienced TEAEs (33.5%) compared with placebo (48.1%), including both Covid-19-related (25.8% vs. 39.7%, respectively) and

non-Covid-19-related (11.0% vs. 16.0%, respectively) events (**Table 3; Table S11**). The most frequent TEAEs and SAEs were related to Covid-19, with a higher proportion of placebo participants with at least one of these events (**Table S11-S12**). Serious TEAEs were reported in 0 participants (0%) in the REGEN-COV group and 4 participants (2.6%) in the placebo group; 1 of the 4 in the placebo group had a non-Covid-19-related serious TEAE (**Table S12**). There were no grade ≥3 injection site reactions or grade ≥3 hypersensitivity reactions in either group (**Table 3**). Injection site reactions (grade 1–2) occurred in 6 participants (4%) in the REGEN-COV group and 1 participant (1%) in the placebo group (**Table S11**). No deaths were reported up to the data cut-off date (March 11, 2021).

Pharmacokinetics

Following SC administration of a single 1200mg dose to study participants, casirivimab (REGN10933) and imdevimab (REGN10987) were rapidly absorbed **Figure S5; Figure S6**), with mean (SD) concentrations in serum one day after dosing of 23.3 (15.0) mg/L and 22.7 (14.8) mg/L. Both antibodies reached maximal concentrations in serum at a median time of 7.5 days. Casirivimab and imdevimab exhibited linear elimination and had a mean (SD) half-life of 30.2 (5.31) days and 26.5 (5.31) days. Mean (SD) concentrations in serum 28 days after dosing (C28) were 33.5 (12.3) mg/L and 26.9 (9.12) mg/L for casirivimab and imdevimab. A summary of PK parameters after a single 1200mg SC dose is shown in **Table S13**.

DISCUSSION

REGEN-COV has previously been shown to have robust efficacy and a positive risk-benefit profile in high-risk, symptomatic individuals infected with SARS-CoV-2: intravenous REGEN-COV 1200mg lowered viral load (-0.71 $\log_{10}$ copies/mL adjusted mean difference vs. placebo at Day 7), decreased duration of symptoms (10 vs. 14 days placebo), and prevented hospitalization or all-cause death (70.4% reduction) in these high risk individuals.[21,22] Additionally, in the companion report from Part A of this trial, subcutaneous REGEN-COV reduced the likelihood of infection (asymptomatic or symptomatic) in individuals at high risk for infection due to cohabitation with a SARS-CoV-2–positive household member. The results of Part B of this study presented here show that individuals identified after SARS-CoV-2 infection has already occurred (i.e., PCR-positive) but prior to developing symptoms also benefit from subcutaneous REGEN-COV as they have a 31.5% reduced likelihood of developing symptomatic disease. Moreover, REGEN-COV reduced symptomatic disease by more than 75% when symptoms began 3 days or longer after treatment, suggesting a greater impact when treatment is provided earlier in the course of infection and that imminent symptomatic disease is less modifiable. From a public health perspective, treatment of early asymptomatic individuals may decrease the overall population burden of high viral load carriage, reducing the reservoir for potential further transmission and virus mutation.[23,24] This trial also demonstrated that subcutaneous administration of REGEN-COV is efficacious with an acceptable safety profile, thus potentially providing substantial benefits by avoiding the healthcare resources necessary for an intravenous infusion.

We propose that asymptomatic, infected individuals who had not yet mounted their own humoral immune response (i.e., asymptomatic/PCR-positive/seronegative) constitute the earliest stages of SARS-CoV-2 infection. Consistent with this notion, a high proportion of asymptomatic/PCR-positive/seronegative individuals treated with placebo went on to develop symptomatic disease, and these individuals also cleared virus levels more slowly than symptomatic/PCR-positive/seronegative individuals treated with placebo from other REGEN-COV trials.[21,22] This suggests that asymptomatic/PCR-positive/seronegative individuals observed in this trial are indeed earlier in their time course and may go on to produce high levels of virus for a longer duration of time. This period of high viral load carriage in untreated, asymptomatic individuals represents a window of time in which the virus may continue to mutate and transmit to other uninfected individuals.[10,16,23]

Although the primary analyses were in seronegative participants, REGEN-COV treatment also provided a benefit in preventing symptomatic infection regardless of baseline serology status, suggesting that treatment of early SARS-CoV-2 infection with the antibody combination is warranted for those with and without evidence of immunity. Point-of-care serology tests may thus have limited utility in guiding treatment decisions in the clinic for this particular population.

The reduction in viral load with subcutaneous REGEN-COV observed here in the early treatment of asymptomatic individuals was comparable to that observed in symptomatic outpatients at high risk for severe Covid-19, thus supporting the similarity of virologic

efficacy of subcutaneous REGEN-COV 1200mg and intravenous REGEN-COV 2400mg and 1200mg (**Figure S3**).[21] The reduction in duration of symptoms with subcutaneous REGEN-COV for those who did become symptomatic in this early treatment study (6 days) was also similar to that observed in symptomatic outpatients (4 days).[21] Although the number of participants who had risk factors for severe Covid-19 was only ~30%, 6 placebo-treated participants had an ER visit or hospitalization while no participants receiving REGEN-COV had these events, consistent with observations showing reduced risk of hospitalization or death in symptomatic outpatients with ≥1 risk factors.[21] Overall, these results demonstrate that 1200mg subcutaneous administration of REGEN-COV has similar antiviral efficacy and clinical benefit as intravenous administration as observed in a study in high-risk outpatients,[21] potentially supporting the early treatment of Covid-19 with either intravenous or subcutaneous administration route.

As has been shown consistently in REGEN-COV clinical studies, a larger proportion of participants who received placebo experienced ≥1 TEAE, with the difference attributed to the higher number of Covid-19-related events observed in that group.[21] Following subcutaneous dosing, concentrations of each antibody in serum were above the predicted neutralization target concentration, based on in vitro and preclinical data, as early as the first day following dosing and throughout the 28-day efficacy assessment period.

REGEN-COV is currently available under emergency use authorization (EUA) for the treatment of symptomatic outpatients at high risk for developing severe Covid-19.[25,26] Despite widespread vaccination and the authorization of monoclonal antibody combinations for outpatient treatment, there are approximately 70,000 cases of Covid-19, 6,000 hospitalizations, and 1,000 deaths in the U.S. every month.[27] Based upon the totality of evidence from phase 3 REGEN-COV clinical studies[21] and previously reported data on REGEN-COV activity against VOC/VOIs,[20] there is rationale for the use of the antibody combination in various settings, from infection prevention to early treatment of asymptomatic individuals and symptomatic, high-risk Covid-19 outpatients. As a complement to vaccines, widespread utilization in these settings – which can be more easily accomplished with a convenient subcutaneous regimen – may dramatically reduce the overall reservoir of virus in the community, as well as decrease disease severity and healthcare utilization in infected individuals.

DATA SHARING

A data sharing statement provided by the authors is available with the full text of this article.

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FINANCIAL DISCLOSURE

Disclosure forms provided by the authors are available with the full text of this article.

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TABLES

Table 1. Demographics and Baseline Characteristics (Seronegative).*

	Placebo (N=106)	REGEN-COV 1200 mg SC (N=101)	Total (N=207)
Age — yr			
Mean	42.5±18.3	39.2±17.7	40.9±18.0
≥50 — no. (%)	39 (36.8)	31 (30.7)	70 (33.8)
Male sex — no. (%)	43 (40.6)	51 (50.5)	94 (45.4)
Race — no. (%)			
White	96 (90.6)	79 (78.2)	175 (84.5)
Black or African American	4 (3.8)	7 (6.9)	11 (5.3)
Asian	3 (2.8)	9 (8.9)	12 (5.8)
American Indian or Alaska Native	0	1 (1.0)	1 (0.5)
Other	3 (2.8)	5 (5.0)	8 (3.9)
Ethnicity — no. (%)			
Hispanic or Latino	38 (35.8)	34 (33.7)	72 (34.8)
Not Hispanic or Latino	67 (63.2)	66 (65.3)	133 (64.3)
Other	1 (0.9)	1 (1.0)	2 (1.0)
Mean weight — kg	78.5±19.04	81.7±22.86	80.1±21.01
Body-mass index†			
Mean	27.8±6.46	28.3±6.68	28.1±6.56
>30 — no. (%)	30 (28.3)	37 (36.6)	67 (32.4)
Participants with any high-risk factor for Covid-19 — no. (%)‡	34 (32.7)	31 (31.0)	65 (31.9)
≥65 years of age	13 (12.5)	8 (8.0)	21 (10.3)
Body-mass index† ≥35 kg/m^2	11 (10.6)	16 (16.0)	27 (13.2)
Chronic kidney disease	3 (2.9)	2 (2.0)	5 (2.5)
Diabetes	11 (10.6)	5 (5.0)	16 (7.8)
Immunosuppressive disease	1 (1.0)	1 (1.0)	2 (1.0)
Receiving immunosuppressive treatment	0	3 (3.0)	3 (1.5)
≥55 years of age with CVD, hypertension, or COPD	15 (14.4)	13 (13.0)	28 (13.7)
Total number of households	99	97	188
Number of households by size§ — no. (%)¶			
1	88 (88.9)	86 (88.7)	174 (92.6)
2	9 (9.1)	9 (9.3)	12 (6.4)
3	2 (2.0)	2 (2.1)	2 (1.1)
>3	0	0	0

*Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, CVD cardiovascular disease, mFAS-B modified full analysis set-B, and SC subcutaneous.
†The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡Percentages based on the seronegative mFAS-B population: placebo (n=104), REGEN-COV (n=100), and total (n=204).
§Household size is calculated by counting the seronegative mFAS-B study participants living in the same household.
¶Percentages based on the total number of households: placebo (n=99), REGEN-COV (n=97), and total (n=188).

Table 2. Primary and Key Secondary Efficacy Endpoints (Seronegative).*

	Placebo (N=104)	REGEN-COV 1200 mg SC (N=100)
Proportion of participants who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP†		
No./total no. (%)	44/104 (42.3)	29/100 (29.0)
Relative risk reduction	-	31.5%
Odds ratio (95% CI)	-	0.54 (0.30–0.97)
P value‡	-	0.0380
No. of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP		
Total no. of weeks	170.3	89.6
Total per 1000 participants — weeks	1637.4	895.7
Reduction§	-	45.3%
P value¶	-	0.0273
Mean per-symptomatic participant — weeks	3.9±4.5	3.1±4.1
Mean per-participant — weeks	1.6±3.5	0.9±2.6
No. of weeks of high viral load (>4 $\log_{10}$ copies/ml) in NP swab samples during the EAP		
Total no. of weeks	82	48
Total duration (weeks) per 1000 participants	811.9	489.8
Reduction§	-	39.7%
P value¶	-	0.0010
Mean per-participant — weeks	0.8±0.8	0.5±0.7

*Plus–minus values are means ±SD. Three seronegative participants (two in placebo group and one in the REGEN-COV group) were excluded from efficacy analyses as they were determined post-randomization to be symptomatic at baseline. Key secondary endpoints are presented in order of the hierarchical testing sequence. EAP denotes efficacy assessment period, NP nasopharyngeal, RT-qPCR quantitative reverse transcription polymerase chain reaction, and SC subcutaneous.
†Primary endpoint.
‡Based on logistic regression model adjusted by region (US vs. ex-US) and age group (12 to less than 50 years of age vs. 50 years of age or older).
§Based on the normalized weeks per 1000 participants.
¶Based on stratified Wilcoxon rank sum test (van Elteren test) with region (US vs. ex-US) and age group (12 to less than 50 years of age vs. 50 years of age or older) as strata.

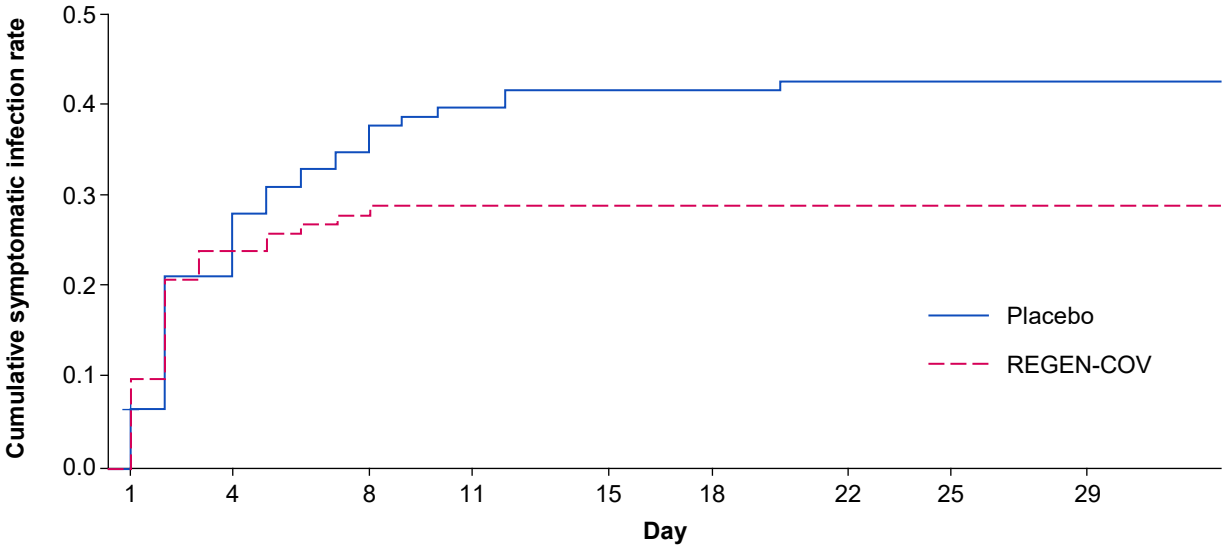
Table 3. Overview of Treatment-Emergent Adverse Events.

	Placebo (N=156)		REGEN-COV 1200 mg SC (N=155)	
n (%)	**Overall**	**Non-Covid-19**	**Overall**	**Non-Covid-19**
No. of TEAEs	109	42	67	26
No. of TEAEs with grade ≥3	5	2	1	1
No. of serious TEAEs	4	1	0	0
No. of AESIs*	0	0	0	0
No. of TEAEs resulting in study drug withdrawal	0	0	0	0
No. of TEAEs resulting in death	0	0	0	0
Participants with at least one TEAE	75 (48.1)	25 (16.0)	52 (33.5)	17 (11.0)
Participants with at least one TEAE with grade ≥3	4 (2.6)	1 (0.6)	1 (0.6)	1 (0.6)
Participants with at least one serious TEAE	4 (2.6)	1 (0.6)	0	0
Participants with at least one AESI*	0	0	0	0
Participants with at least one TEAE resulting in study drug withdrawal	0	0	0	0
Participants with at least one TEAE resulting in death	0	0	0	0

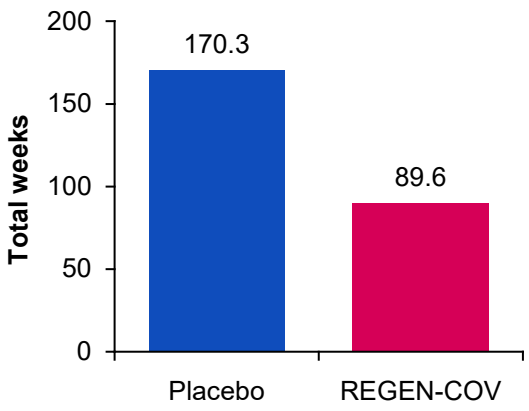
AESI denotes adverse event of special interest, SC subcutaneous, and TEAE treatment-emergent adverse event.
*Grade ≥3 injection site reactions or hypersensitivity reactions.

Figure 1. Prevention of Symptomatic Infection with REGEN-COV

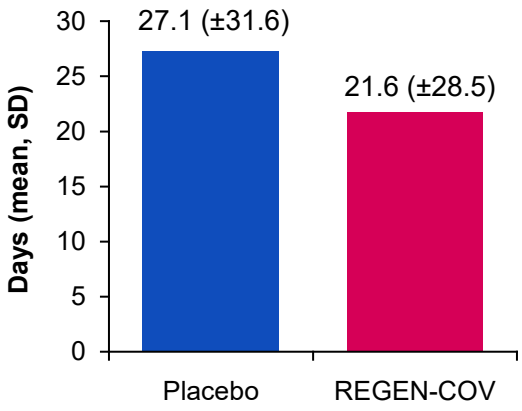
A. Time to First Symptom with an Onset within 14 Days of a Positive RT-qPCR at Baseline or During the Efficacy Assessment Period*



B. Total Weeks of Symptomatic SARS-CoV-2 Infection† by Arm*



C. Mean Number of Days of Symptomatic SARS-CoV-2 Infection† Per Symptomatic Participant*



*Seronegative modified full analysis set-B.
†Within 14 days of a positive RT-qPCR at baseline or during the efficacy assessment period.
RT-qPCR, reverse transcriptase quantitative polymerase chain reaction; SD, standard deviation.

Figure 1. Prevention of Symptomatic Infection with REGEN-COV.

A. Time to First Symptom with an Onset within 14 Days of a Positive RT-qPCR at Baseline or During the Efficacy Assessment Period*

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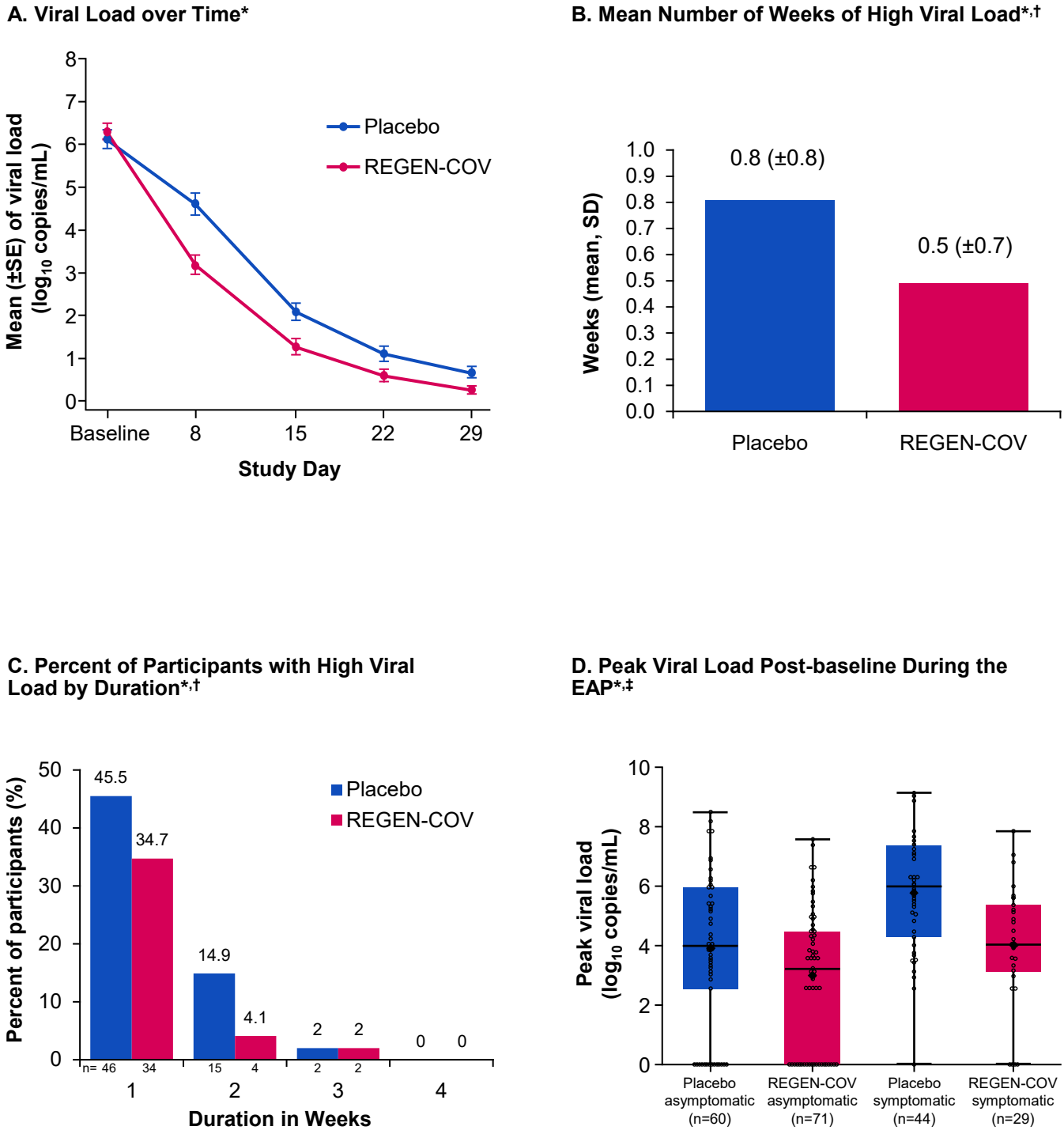
RT-qPCR, reverse transcriptase quantitative polymerase chain reaction; SD, standard deviation.

Figure 2. Reduction in Viral Load with REGEN-COV



*Seronegative modified full analysis set-B. Only non-missing available nasopharyngeal swab viral load data are used for the analysis of viral load endpoints. Only participants with at least one post-baseline viral load data point (in nasopharyngeal swab samples) are included in the analysis.
†High viral load was defined as >4 $\log_{10}$ copies per milliliter.
‡Lines in the boxes represent the median; large, bolded dots in the boxes represent the mean; bottom and top of boxes represent quartiles 1 (25th percentile) and 3 (75th percentile), respectively; whiskers represent the maximum and minimum.
EAP, efficacy assessment period; SD, standard deviation; SE, standard error.

Figure 2. Reduction in Viral Load with REGEN-COV.

A. Viral Load over Time*

B. Mean Number of Weeks of High Viral Load*,†

C. Percent of Participants with High Viral Load by Duration*,†

D. Peak Viral Load Post-baseline During the EAP*,‡

*Seronegative modified full analysis set-B. Only non-missing available nasopharyngeal swab viral load data are used for the analysis of viral load endpoints. Only participants with at least one post-baseline viral load data point (in nasopharyngeal swab samples) are included in the analysis.

†High viral load was defined as >4 $\log_{10}$ copies per milliliter.

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EAP, efficacy assessment period; SD, standard deviation; SE, standard error.