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REGEN-COV Antibody Cocktail in Outpatients with Covid-19

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ABSTRACT

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Background: REGEN-COV (casirivimab and imdevimab) antibody cocktail reduced SARS-CoV-2 viral load in descriptive analyses of the first 275 Covid-19 outpatients in the phase 1/2 portion of an ongoing double-blind, seamless phase 1/2/3 trial.

Methods: This final analysis of the phase 1/2 portion includes 799 patients: 275 (group-1) and 524 (group-2). Patients were randomized (1:1:1) to placebo, 2400mg REGEN-COV, or 8000mg REGEN-COV, and characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody-positive/negative). Efficacy was assessed in patients with a positive baseline RT-qPCR result; safety was assessed in all treated patients. Prespecified hierarchical analyses of virologic endpoints in group-2 were performed to confirm previously reported descriptive analyses from group-1. The proportion of patients with ≥ 1 Covid-19-related medically-attended visit (MAV) through day 29 was assessed in group-1+2.

Results: Time-weighted average reduction in viral load (\log_{10} copies/ml) through day 7 was significantly greater with REGEN-COV (combined 2400mg+8000mg dose groups) versus placebo in patients with baseline viral load $>10^7$ copies/ml (prespecified primary endpoint): -0.68 (95% CI, -0.94 to -0.41; $P<0.0001$). This reduction was -0.73 ($P<0.0001$) in serum antibody-negative patients and -0.36 ($P=0.0003$) in the overall population. Proportions of patients with ≥ 1 Covid-19-related MAV were 2.8% (12/434) with REGEN-COV versus 6.5% (15/231) with placebo ($P=0.024$; relative risk reduction=57%), with greater relative risk reductions in MAVs in patients with ≥ 1 risk factor for hospitalization (71%). Adverse events were similar across groups.

Conclusions: REGEN-COV treatment of outpatients significantly reduced SARS-CoV-2 viral load and Covid-19-related medically-attended visits.

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INTRODUCTION

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first emerged in China in December 2019.^{1,2} Covid-19 severity varies widely among patients, ranging from mild symptoms to severe disease requiring hospitalization or leading to death.³⁻⁷ SARS-CoV-2 viral load has been associated with disease severity and mortality.^{8,9} Treatments that reduce viral burden may improve Covid-19 clinical outcomes.

REGEN-COV (casirivimab and imdevimab; previously REGN-COV2) is a fully-human, neutralizing monoclonal antibody combination therapy directed against the receptor binding domain (RBD) of the SARS-CoV-2 spike (S) protein.¹⁰ Because of previous experience with the emergence of viral variants resistant to a treatment consisting of a single monoclonal antibody (ie, viral escape),¹¹ we pursued a “cocktail” approach. The two antibodies, casirivimab (REGN10933) and imdevimab (REGN10987), bind simultaneously and non-competitively to the RBD of the S protein and have been shown to protect against viral escape in preclinical studies.¹² Importantly, the REGEN-COV cocktail retains its potent in vitro neutralizing activity against emerging viral variants – such as those first identified in the UK (B.1.1.7) and South Africa (B.1.351) – that are resistant to other single and combination antibody treatments.¹³ In vivo efficacy of REGEN-COV was previously demonstrated in two animal models (rhesus macaques and golden hamsters) as evidenced by reduced viral load in both models, reduced virus-induced lung pathology in rhesus macaques, and protection from weight loss in golden hamsters.¹⁴ In the initial descriptive interim analysis of the first 275 Covid-19 outpatients from the ongoing phase 1/2/3 trial reported herein, we previously reported

that administration of the REGEN-COV antibody cocktail rapidly reduced viral load, with greater reductions in those who had not yet mounted an endogenous immune response or had a high viral load at baseline.¹⁵ Here we describe the confirmatory prespecified virologic results of a subsequent phase 2 analysis in 524 additional outpatients with Covid-19, as well as the final phase 1/2 analysis of clinical and safety outcomes in all 799 outpatients.

METHODS

TRIAL DESIGN

This is an ongoing, adaptive, multicenter, randomized, double-blind, placebo-controlled, seamless phase 1/2/3 trial in Covid-19 outpatients (NCT04425629). The trial continues to recruit beyond the 799 patients for whom data are described in this report; phase 3 results will be reported at trial completion.

The phase 1/2 trial design was previously described.¹⁵ Patients were randomly assigned (1:1:1) to receive placebo, 2400mg REGEN-COV (1200mg each of casirivimab and imdevimab; low dose), or 8000mg REGEN-COV (4000mg each of casirivimab and imdevimab; high dose) (Figure S1). The 29-day phase 2 trial included a screening/baseline period (days -1 to 1), a follow-up period (days 2 to 25), and an end-of-study visit (day 29). The phase 1 and 2 portions of the trial were identical, except for additional pharmacokinetic analyses in phase 1.

PATIENTS

Eligible patients were ≥ 18 years of age and nonhospitalized, with a confirmed SARS-CoV-2–positive nasopharyngeal (NP) polymerase chain reaction (PCR) test result ≤ 72 hours and symptom onset ≤ 7 days before randomization. Randomization was stratified by country and presence or absence of ≥ 1 risk factor for severe Covid-19: age > 50 years, obesity (BMI > 30), immunosuppression, and chronic cardiovascular, metabolic, liver, kidney, or lung disease. The full list of inclusion and exclusion criteria was previously described.¹⁵

All patients were assessed for the presence or absence of anti-SARS-CoV-2 antibodies: anti-spike [S1] IgA, anti-spike [S1] IgG, and anti-nucleocapsid IgG. Because these results were not available at randomization, patients underwent randomization regardless of their baseline serum antibody status and were subsequently grouped for analyses as serum antibody–negative (if all available tests were negative), serum antibody–positive (if any of the tests were positive), or unknown (missing or inconclusive results).

INTERVENTION AND ASSESSMENTS

At baseline (day 1), casirivimab and imdevimab (diluted in a 250-ml normal saline solution for co-administration) or saline placebo was administered intravenously over a period of 1 hour. See protocol for schedule of assessments (Supplementary Appendix).

ENDPOINTS

The primary virologic endpoint and two key secondary clinical endpoints were prespecified in this phase 1/2 analysis and tested hierarchically as described in Table S1. The primary virologic endpoint was defined as the time-weighted average change in viral load (\log_{10} copies/ml) from baseline (day 1) through day 7. The two key secondary clinical endpoints were (1) the proportion of patients through day 29 with ≥ 1 Covid-19-related medically-attended visit (MAV), defined as a hospitalization or ER, urgent care, or physician office/telemedicine visit that was confirmed by the investigator to be related

to Covid-19 and (2) the proportion of patients through day 29 with ≥ 1 Covid-19-related MAV consisting of only hospitalization or emergency room (ER) or urgent care visit.

Safety endpoints for the phase 1/2 portion of the trial included adverse events that occurred or worsened during the observation period (assessed in phase 1 only; grade 3 and 4), serious adverse events (SAEs), and adverse events of special interest (AESIs): grade ≥ 2 hypersensitivity or infusion-related reactions.

TRIAL OVERSIGHT

Regeneron designed the trial and, with the trial investigators, gathered the data. Regeneron analyzed the data. The investigators, site personnel, and Regeneron were unaware of the treatment-group assignments. An independent data and safety monitoring committee monitored unblinded data to make recommendations about trial modification and termination.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

STATISTICAL ANALYSIS

The statistical analysis plan for the presented analysis was finalized prior to database lock and unblinding of the additional 524-patient phase 2 dataset. The full analysis set (FAS) included patients with Covid-19 symptoms who underwent randomization.

Patients with a positive SARS-CoV-2 NP PCR test ≤ 72 hours from randomization (baseline) but negative by central lab qualitative PCR at baseline (limit of detection, 714 copies/ml) were excluded from analyses of virologic and clinical endpoints in a modified full analysis set (mFAS). Subgroup analyses by baseline serum antibody-status and baseline viral load were based on previous descriptive analyses from placebo-treated patients in this study¹⁵ and were prespecified. Safety was assessed in patients in the FAS who received study drug (active or placebo).

A previous descriptive analysis reported virologic and clinical efficacy data in the first 275 patients enrolled in the trial (analysis group-1).¹⁵ To confirm the virologic efficacy seen in group-1, analyses of virologic endpoints were conducted using data from patients 276 through 799 (524 patients; analysis group-2). Analyses of clinical endpoints and safety utilized data from all available patients, inclusive of the first 275 patients (patients 1 through 799; group-1+2).

The virologic efficacy endpoint was calculated as previously described (see also Supplementary Appendix).¹⁵ Key secondary clinical endpoints were analyzed using Fisher's exact test. Analyses of the primary virologic and two key clinical endpoints were conducted at a two-sided $\alpha=0.05$ utilizing a hierarchical testing strategy to control for type I error. Statistical analyses were performed with SAS software, version 9.4 or

higher (SAS Institute). Additional methods are described in the Supplementary Appendix.

RESULTS

BASELINE CHARACTERISTICS

Between June 16, 2020 and September 23, 2020, 799 symptomatic patients underwent randomization in the phase 1/2 portion of the trial: 266, 267, and 266 patients were assigned to receive low-dose REGEN-COV, high-dose REGEN-COV, or placebo, respectively (Figure S2). Among the 799 patients in group-1+2, 87 (10.9%) tested negative in the central lab SARS-CoV-2 NP RT-qPCR assay at baseline and 47 (5.9%) were without central lab baseline viral load data; consequently, the mFAS set comprised 665 patients. Similarly, among the 524 patients in group-2 (primary virologic efficacy analysis), the mFAS set comprised 437 patients.

Of the 799 randomized patients, the median age was 42.0 years, 47.1% were male, 9.3% identified as Black or African American, and 50.4% identified as Hispanic or Latino (Table 1). Four-hundred and eighty-three (60.5%) patients had ≥ 1 risk factor for hospitalization due to Covid-19, including obesity (BMI >30 ; 37.3%), age >50 years (29.3%), cardiovascular disease (20.5%), or chronic metabolic disease (13.1%). Baseline characteristics were similar between the 275-patient group-1 and 524-patient group-2 (Table S2).¹⁵

At randomization, 408 (51.1%) patients were serum antibody-negative, 304 (38.0%) were serum antibody-positive, and 87 (10.9%) were serum antibody-unknown. Median baseline viral load was 5.48 \log_{10} copies/ml (47 of 799 with missing baseline data); 256 (32.0%) patients had baseline viral load $>10^7$ copies/ml. The mean time from symptom onset to randomization was 3.4 days in the overall trial population: 3.3 days in serum

antibody-negative patients; 3.6 days in serum antibody-positive patients; 2.9 days in patients with viral load $>10^7$ copies/ml; and 3.8 days in patients with viral load $\leq 10^7$ copies/ml. Among 408 patients with ≥ 1 risk factor for hospitalization in the mFAS, 336 (82.4%) were serum antibody-negative or had viral load $>10^4$ copies/ml.

NATURAL HISTORY

Patients in the placebo arm who were serum antibody-negative at baseline had higher median viral loads at baseline compared to those who were serum antibody-positive (7.73 \log_{10} copies/ml versus 3.88 \log_{10} copies/ml), and they took substantially longer to bring their viral levels to the lower limit of quantification or to undetectable (Figure S3; Figure S4). Similarly, for clinical outcomes, placebo patients who were serum antibody-negative at baseline had substantially higher rates of Covid-19-related MAVs (9.7%; 12/124) than placebo patients who were serum antibody-positive at baseline (2.4%; 2/83) (Figure S5). As the endogenous immune response was associated with baseline viral titers, there was the expected association of Covid-19-related MAV risk with baseline viral load as well as with presence of risk factors: MAVs occurred in 0% (0/55) of patients with baseline viral load $\leq 10^4$ copies/ml versus 8.5% (15/176) with baseline viral load $>10^4$ copies/ml and MAVs occurred in 2.2% (2/89) of patients with no risk factors versus 9.2% (13/142) with ≥ 1 risk factor.

VIROLOGIC EFFICACY

Prespecified comparisons for the virologic efficacy endpoint were assessed hierarchically in the 524-patient group-2 who were confirmed SARS-CoV-2-positive by

NP RT-qPCR at baseline (mFAS; n=437) (Table S1; Table 2). REGEN-COV treatment significantly reduced viral load through day 7 versus placebo in all prespecified virologic efficacy comparisons (Table 2; Figure 1; Figure S6). In the first comparison, among patients with baseline viral load $>10^7$ copies/ml, the least-squares mean difference between REGEN-COV treatment (combined 2400mg and 8000mg dose groups) and placebo in the time-weighted average (TWA) daily change in viral load through day 7 was $-0.68 \log_{10}$ copies/ml (95% CI, -0.94 to -0.41 ; $P<0.0001$) (Table 2; Figure S6). Similarly, the least-squares mean difference in TWA daily change in viral load through day 7 with REGEN-COV treatment and placebo was $-0.73 \log_{10}$ copies/ml (95% CI, -0.97 to -0.48 ; $P<0.0001$) in patients who were serum antibody-negative at baseline, while it was $-0.36 \log_{10}$ copies/ml (95% CI, -0.56 to -0.16 ; $P=0.0003$) in the overall mFAS (Table 2; Figure S6). Treatment effects were similar with the low-dose and high-dose antibody cocktail across all virologic efficacy endpoint comparisons (Table 2; Figure S6). Results from additional key virologic endpoints are provided in Table S3, Figure S7, and Figure S8.

CLINICAL EFFICACY

There were two clinical efficacy endpoints prespecified for hierarchical testing: the proportion of patients with at least one Covid-19-related MAV and the proportion of patients with at least one Covid-19-related MAV consisting of only hospitalization or ER or urgent care visits (Table S1; Table 2). Both endpoints were assessed through day 29 in the pooled 799-patient group (group-1+2) who were confirmed SARS-CoV-2-positive by NP RT-qPCR at baseline (mFAS; n=665). Overall, 67% of the Covid-19-related

MAVs were hospitalizations or ER visits (30% and 37%, respectively), 26% physician office/telemedicine visits, and 7% urgent care visits. Descriptions of Covid-19-related MAVs are included in Table S4.

The proportion of patients in the REGEN-COV treatment group (combined 2400mg and 8000mg dose groups) with ≥ 1 Covid-19-related MAV was 2.8% (12 of 434) compared to 6.5% (15 of 231) in the placebo group, which represents a relative reduction of 57% (absolute difference vs. placebo, -3.7 percentage points; 95% CI, -8% to 0%; $P=0.0240$) (Table 2). Treatment effects observed with REGEN-COV were more pronounced in baseline serum antibody-negative patients (3.4% versus 9.7% placebo; 65% relative reduction) (Table S5). For the final hierarchical endpoint, the proportion of patients with Covid-19-related hospitalization or ER or urgent care visits was numerically lower in the REGEN-COV combined dose group (vs placebo) but the difference did not reach statistical significance (Table 2). Post-hoc analyses demonstrated a reduction in the proportion of antibody cocktail-treated patients (combined dose group) who were hospitalized or died (0.7% [3 of 434] versus 2.2% [5 of 231] placebo; relative reduction of 68%) and in those who were hospitalized or had an ER visit (1.8% [8 of 434] versus 4.3% [10 of 231] placebo; relative reduction of 57%) (Table S6).

Additional post hoc analyses investigated the effects of the antibody cocktail treatment on MAVs in various high-risk subgroups. The proportion of patients with ≥ 1 risk factor for hospitalization ($n=408$) who had ≥ 1 Covid-19-related MAV in the REGEN-COV group (combined dose group) versus the placebo group was: 2.6% versus 9.2% (absolute

difference vs. placebo, -6.5 percentage points; 95% CI, -13 to -2; 71% relative reduction) (Figure 2; Table S7). The proportion of patients with ≥ 1 risk factor who were baseline serum antibody-negative and had a viral load $>10^4$ copies/ml ($n=217$) who had ≥ 1 Covid-19-related MAV in the REGEN-COV group (combined dose group) versus the placebo group was: 2.1% versus 13.2% (absolute difference vs. placebo, -11.0 percentage points; 95% CI, -21 to -3; 84% relative reduction) (Table S8). The majority (59%) of patients who experienced a MAV had a viral load of $\geq 4 \log_{10}$ copies/ml around the time of the MAV (Table S4; Figure S9). As with the virologic endpoints, no meaningful differences in clinical outcomes were observed between low-dose and high-dose treatments.

SAFETY

SAEs were experienced by 4 of 258 patients (1.6%) in the REGEN-COV 2400mg group, 2 of 260 patients (0.8%) in the REGEN-COV 8000mg group, and a higher number of patients (ie, 6 of 262 patients [2.3%]) in the placebo group (Table 3; Table S9). All SAEs were considered to be due to advanced or progressive Covid-19 disease and/or associated concomitant clinical conditions and were not evaluated to be related to the study drug treatment.

AESIs – grade ≥ 2 infusion-related reactions and hypersensitivity reactions – that occurred or worsened during the safety observation period were reported in no patients in the 2400mg group, 4 (1.5%) patients in the 8000mg group, and 2 (0.8%) patients in the placebo group (Table 3; Table S9).

PHARMACOKINETICS

The mean concentrations for casirivimab and imdevimab increased in a dose-proportional manner and were consistent with linear pharmacokinetics for single intravenous doses (Table S10). The mean \pm SD day 29 concentrations of casirivimab and imdevimab in serum were 79.7 \pm 34.6 and 65.2 \pm 28.1 mg/L, respectively, for the low (1200mg) doses and 250 \pm 97.4 and 205 \pm 82.7 mg/L, respectively, for the high (4000mg) doses (Table S10).

DISCUSSION

The findings from this final phase 1/2 analysis of REGEN-COV antibody cocktail for the treatment of outpatients with Covid-19 confirm and extend the findings from the first 275 patients.¹⁵ To better understand the natural history of Covid-19 in outpatients, data from placebo patients in this trial were examined. This data confirms previous findings that patients who at baseline had not yet mounted their own immune response (ie, serum antibody-negative) had median viral loads at baseline that were almost 3 log copies/ml higher compared to patients who were serum antibody-positive, and took longer to reach low or undetectable levels.¹⁵⁻¹⁷ Similar to other viral infections, such as HIV,¹⁸ ebola virus,¹⁹ and influenza,²⁰ high viral load appears to be a predictor of disease progression in Covid-19, as evidenced by the fact that Covid-19-related MAVs were more frequent in placebo patients with baseline viral loads $>10^4$ copies/ml. The data also indicate that risk factors for severe disease, such as older age and obesity, may help to predict outpatients who are most likely to have a subsequent Covid-19-related MAV. For example, 9.2% (13/142) of placebo patients with ≥ 1 risk factor had a MAV compared to 2.2% (2/89) of placebo patients without any risk factors. In this trial, $>80\%$ of patients with risk factors were serum antibody-negative or had a viral load $>10^4$ copies/ml. In the absence of a rapid serology test or quantitative PCR assay to identify at-risk patients, those with risk factors for hospitalization would be most likely to benefit from early treatment with the antibody cocktail.

The prespecified hierarchical analysis described herein prospectively and with high statistical significance replicates and confirms the virologic efficacy of REGEN-COV as previously reported in an earlier descriptive analysis, and reveals similar virologic

efficacy with both the 2400mg and 8000mg doses of the antibody cocktail.¹⁵ The reduction in viral load was greatest in the first 5 days after treatment, in patients who were serum antibody-negative or who had high viral load at baseline.

The reduction in viral load after treatment with either dose of REGEN-COV was accompanied by a significant reduction in the proportion of patients requiring a subsequent Covid-19-related MAV, the majority (67%) of which were hospitalizations or ER visits. REGEN-COV antibody cocktail treatment led to a 57% relative reduction in MAVs (6.5% placebo versus 2.8% combined dose group; $P=0.0240$). Interestingly, the reduction in the proportion of patients with MAVs treated with REGEN-COV compared to placebo occurred only after the first week of treatment. One possible explanation for this finding is that MAVs occurring in the first week are not modifiable despite accelerated clearance of the virus. Indeed, among patients treated with the antibody cocktail, all 3 hospitalizations occurred in the first 3 days after treatment when viral loads were still $\geq 4 \log_{10}$ copies/ml but no hospitalizations occurred after day 7 (Table S4; Figure S9). In contrast, among patients treated with placebo, 3 of the 5 hospitalizations occurred after day 7, when viral loads continued to be high ($\geq 4 \log_{10}$ copies/ml). These data support early identification and rapid treatment of outpatients with Covid-19 in order to optimize the efficacy of REGEN-COV treatment.

The safety of REGEN-COV antibody cocktail was as previously reported.¹⁵ A low incidence of SAEs, infusion-related reactions, and hypersensitivity reactions was observed. Similar to results reported previously,¹⁵ concentrations of each antibody in

serum at day 29 were well above the predicted neutralization target concentration based on in vitro and preclinical data.

REGEN-COV antibody cocktail at the 2400mg dose received Emergency Use Authorization (EUA) from the US FDA in November 2020 for the treatment of mild-to-moderate COVID-19.²¹ The clinical evidence from this trial suggests that treatment has the greatest benefit when given to high-risk patients who present early after diagnosis when they are most likely to have high viral load. There were no adverse findings observed in patients who were serum antibody-positive at baseline. In this pandemic, early treatment of Covid-19 outpatients is crucial and, if unable to rapidly determine viral load or serum antibody status, the risk-benefit assessment supports treatment to prevent MAVs in high-risk patients.

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. Demographic and Baseline Medical Characteristics* (N=799; Full Analysis Set)

Characteristic	Total (N=799)	Placebo (N=266)	REGEN-COV 2400 mg (N=266)	REGEN-COV 8000 mg (N=267)	REGEN-COV combined (N=533)
Median age (IQR) — yr	42.0 (31.0–52.0)	42.0 (32.0–53.0)	42.0 (31.0–52.0)	42.0 (30.0–52.0)	42.0 (30.0–52.0)
Male sex — no. (%)	376 (47.1)	134 (50.4)	122 (45.9)	120 (44.9)	242 (45.4)
Hispanic or Latino ethnic group — no. (%)†	403 (50.4)	137 (51.5)	132 (49.6)	134 (50.2)	266 (49.9)
Race — no. (%)†					
White	681 (85.2)	227 (85.3)	224 (84.2)	230 (86.1)	454 (85.2)
Black or African American	74 (9.3)	24 (9.0)	27 (10.2)	23 (8.6)	50 (9.4)
Asian	14 (1.8)	4 (1.5)	6 (2.3)	4 (1.5)	10 (1.9)
American Indian or Alaska Native	5 (0.6)	3 (1.1)	1 (0.4)	1 (0.4)	2 (0.4)
Unknown	7 (0.9)	3 (1.1)	1 (0.4)	3 (1.1)	4 (0.8)
Not reported	18 (2.3)	5 (1.9)	7 (2.6)	6 (2.2)	13 (2.4)
Median weight (IQR) — kg	81.60 (69.90–95.30)	81.80 (70.80–94.30)	81.60 (69.90–94.50)	81.20 (68.00–97.10)	81.60 (69.30–95.30)

Body-mass index‡	29.67±8.228	29.96±10.460	29.51±6.413	29.57±7.355	29.54±6.890
Obesity — no. (%)§	298 (37.3)	93 (35.0)	101 (38.0)	104 (39.0)	205 (38.5)
Baseline viral load in nasopharyngeal swab (raw values)					
No. of patients	752	259	243	250	493
Mean viral load — copies/ml	18719108.2± 28449769.31	20949819.7± 30172071.11	17403960.8± 27210806.40	17686414.3± 27755446.26	17547192.8± 27460771.64
Median viral load (range) — copies/ml	304500.0 (1–71000000)	437000.0 (1–71000000)	295000.0 (1–71000000)	262500.0 (1–71000000)	270000.0 (1–71000000)
Baseline viral load in nasopharyngeal swab (log ₁₀ scale)					
No. of patients	752	259	243	250	493
Mean viral load — log ₁₀ copies/ml	5.16±2.500	5.21±2.511	5.23±2.449	5.05±2.544	5.14±2.497
Median viral load (range) — log ₁₀ copies/ml	5.48 (0.0–7.9)	5.64 (0.0–7.9)	5.47 (0.0–7.9)	5.42 (0.0–7.9)	5.43 (0.0–7.9)
Baseline viral load in nasopharyngeal swab category – no. (%)					
>10 ⁴	523 (65.5)	176 (66.2)	180 (67.7)	167 (62.5)	347 (65.1)
>10 ⁵	439 (54.9)	149 (56.0)	148 (55.6)	142 (53.2)	290 (54.4)
>10 ⁶	332 (41.6)	114 (42.9)	110 (41.4)	108 (40.4)	218 (40.9)
>10 ⁷	256 (32.0)	93 (35.0)	82 (30.8)	81 (30.3)	163 (30.6)

Positive baseline qualitative RT-PCR — no. (%)	665 (83.2)	231 (86.8)	215 (80.8)	219 (82.0)	434 (81.4)
Baseline serum C-reactive protein level					
No. of patients	600	203	200	197	397
Mean level — mg/l	13.930±28.8461	19.449±37.5595	10.991±24.1638	11.227±21.1793	11.108±22.7035
Median level (range) — mg/l	3.750 (0.10–239.67)	4.860 (0.10–232.04)	3.240 (0.12–239.67)	3.420 (0.14–157.96)	3.320 (0.12–239.67)
Baseline serum antibody status — no. (%)					
Negative	408 (51.1)	134 (50.4)	140 (52.6)	134 (50.2)	274 (51.4)
Positive	304 (38.0)	106 (39.8)	96 (36.1)	102 (38.2)	198 (37.1)
Unknown	87 (10.9)	26 (9.8)	30 (11.3)	31 (11.6)	61 (11.4)
Symptom onset to randomization					
No. of patients	698	240	222	236	458
Median time from symptom onset to randomization (IQR) — days	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)
At least one risk factor for hospitalization — no. (%)¶	483 (60.5)	158 (59.4)	165 (62.0)	160 (59.9)	325 (61.0)

* Plus–minus values are means \pm SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, RT-PCR reverse-transcriptase polymerase chain reaction, and SD standard deviation.

† Race and ethnic group were reported by the patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Obesity is defined as a body-mass index of greater than 30.

¶ Risk factors for hospitalization include an age of more than 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised (immunosuppression or receipt of immunosuppressants).

Table 2. Key Virologic and Clinical End Points

End Point	Placebo	REGEN-COV 2400mg	REGEN-COV 8000mg	REGEN-COV combined
Time-weighted average change from baseline in viral load* (log₁₀ copies/ml) from day 1 through day 7 (analysis group 2)				
Baseline viral load >10⁷ copies/ml (mFAS)				
No. of patients	70	58	52	110
Least-squares mean change (SE) — log ₁₀ copies/ml	-1.46 (0.15)	-2.14 (0.16)	-2.13 (0.16)	-2.13 (0.13)
95% CI	-1.75, -1.16	-2.44, -1.83	-2.44, -1.82	-2.39, -1.87
Difference vs. placebo at day 7 — log ₁₀ copies/ml				
Least-squares mean (SE)		-0.68 (0.16)	-0.68 (0.16)	-0.68 (0.14)
95% CI† (P value)		-0.99, -0.37 (<0.0001)	-0.99, -0.36 (<0.0001)	-0.94, -0.41 (<0.0001)
Baseline viral load >10⁶ copies/ml (mFAS)				
No. of patients	86	72	73	145
Least-squares mean change (SE) — log ₁₀ copies/ml	-1.40 (0.13)	-2.13 (0.13)	-1.98 (0.13)	-2.06 (0.11)
95% CI	-1.65, -1.14	-2.38, -1.88	-2.24, -1.72	-2.27, -1.85
Difference vs. placebo at day 7 — log ₁₀ copies/ml				
Least-squares mean (SE)		-0.73 (0.14)	-0.58 (0.14)	-0.65 (0.12)
95% CI† (P value)		-1.01, -0.45 (<0.0001)	-0.86, -0.30 (<0.0001)	-0.89, -0.41 (<0.0001)
Baseline serum antibody status: negative (mFAS)				
No. of patients	93	80	77	157

Least-squares mean change (SE) — log ₁₀ copies/ml	-1.18 (0.10)	-1.92 (0.11)	-1.90 (0.11)	-1.91 (0.08)
95% CI	-1.38, -0.99	-2.13, -1.71	-2.11, -1.69	-2.06, -1.76
Difference vs. placebo at day 7 — log ₁₀ copies/ml				
Least-squares mean (SE)		-0.74 (0.14)	-0.71 (0.14)	-0.73 (0.12)
95% CI† (P value)		-1.02, -0.45 (<0.0001)	-1.00, -0.43 (<0.0001)	-0.97, -0.48 (<0.0001)
mFAS				
No. of patients	146	137	141	278
Least-squares mean change (SE) — log ₁₀ copies/ml	-1.30 (0.09)	-1.69 (0.09)	-1.64 (0.09)	-1.66 (0.07)
95% CI	-1.49, -1.12	-1.87, -1.50	-1.82, -1.46	-1.81, -1.52
Difference vs. placebo at day 7 — log ₁₀ copies/ml				
Least-squares mean (SE)		-0.38 (0.12)	-0.34 (0.12)	-0.36 (0.10)
95% CI† (P value)		-0.61, -0.15 (0.0011)	-0.57, -0.11 (0.0035)	-0.56, -0.16 (0.0003)
Proportion of patients with Covid-19-related MAVs through day 29 (analysis groups 1+2)				
mFAS				
No. of patients	231	215	219	434
Patients with ≥1 visit within 29 days — no. (%)	15 (6.5)	6 (2.8)	6 (2.7)	12 (2.8)
Difference vs. placebo — percentage points		-3.7	-3.8	-3.7
95% CI† (P value)		-8.0, 0.3 (0.0754)	-8.1, 0.2 (0.0737)	-7.9, -0.3 (0.0240)
Proportion of patients with subset of Covid-19-related MAVs consisting only of hospitalization or ER visit or urgent care visit through day 29 (analysis groups 1+2)				
mFAS				

No. of patients	231	215	219	434
Patients with ≥ 1 visit within 29 days — no. (%)	10 (4.3)	5 (2.3)	5 (2.3)	10 (2.3)
Difference vs. placebo — percentage points		-2.0	-2.0	-2.0
95% CI† (P value)		-11.2, 7.3 (0.2983)	-11.3, 7.2 (0.2962)	-10.0, 6.0 (0.1575)

* The time-weighted mean change in viral load was based on an analysis of covariance model with treatment group, risk factor, and baseline antibody status as fixed effects and baseline viral load and treatment group-by-baseline viral load as covariates. Confidence intervals were not adjusted for multiplicity.

† Confidence intervals for the difference (REGEN-COV minus placebo) were based on the exact method and were not adjusted for multiplicity.

Table 3. Overview of Serious Adverse Events and Adverse Events of Special Interest in the Safety Population

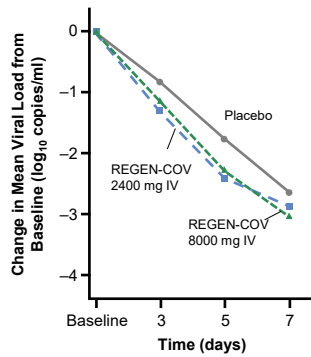
Event	Placebo (N=262)	REGEN-COV 2400mg (N=258)	REGEN-COV 8000mg (N=260)	REGEN-COV combined (N=518)
<i>no. of patients (percent)</i>				
Any serious adverse event	6 (2.3)	4 (1.6)	2 (0.8)	6 (1.2)
Any adverse event of special interest*	2 (0.8)	0	4 (1.5)	4 (0.8)
Any serious adverse event of special interest*	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days	1 (0.4)	0	4 (1.5)	4 (0.8)
Grade ≥2 hypersensitivity reaction within 29 days	2 (0.8)	0	0	0
Patients with adverse events that occurred or worsened during the observation period†				
Patients with grade 3 or 4 event	4 (1.5)	3 (1.2)	2 (0.8)	5 (1.0)
Patients with adverse event that led to death	0	0	0	0
Patients with adverse event that led to withdrawal from the trial	0	0	1 (0.4)	1 (0.2)
Patients with adverse event that led to infusion interruption*	1 (0.4)	0	1 (0.4)	1 (0.2)

* Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions.

† Events listed here were not present at baseline or were an exacerbation of a preexisting condition that occurred during the observation period, which is defined as the time from administration of REGEN-COV or placebo to the final follow-up visit.

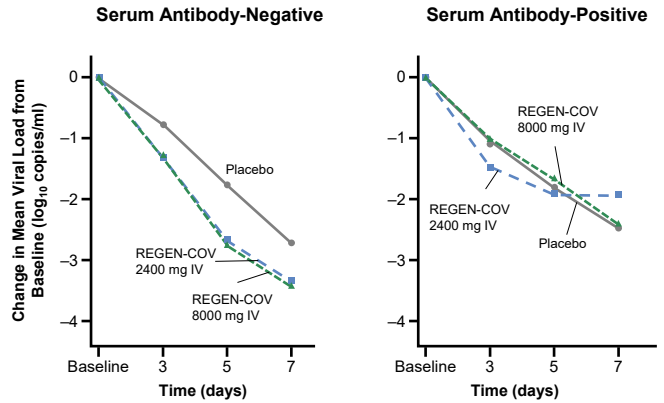
Figure 1. SARS-CoV-2 Viral Load Over Time

A. Viral Load over Time in the Overall Population



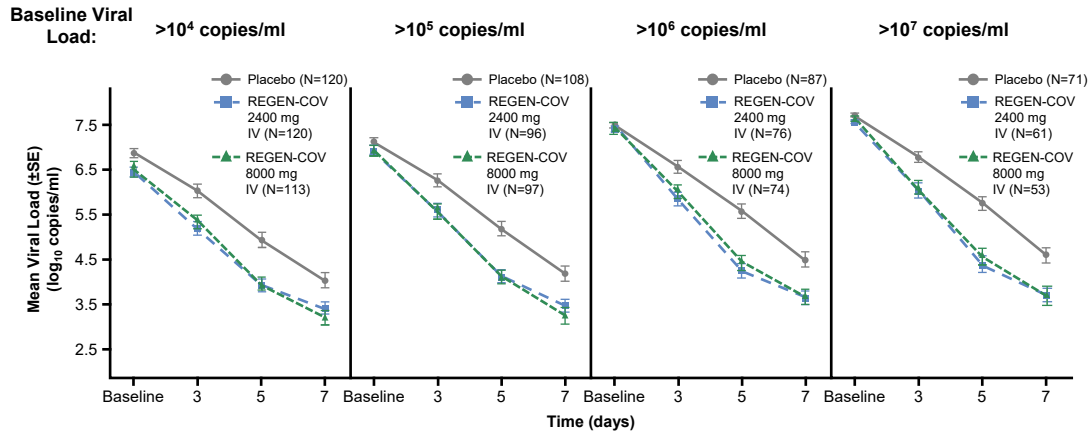
No. at Risk	Baseline	3	5	7
Placebo	150	136	143	146
REGEN-COV 2400 mg IV	142	132	137	137
REGEN-COV 8000 mg IV	145	135	140	141

B. Viral Load over Time According to Baseline Antibody Status



No. at Risk	Baseline	3	5	7	Baseline	3	5	7
Placebo	94	87	91	93	42	39	40	41
REGEN-COV 2400 mg IV	83	78	80	80	45	42	45	45
REGEN-COV 8000 mg IV	79	73	76	77	50	49	50	50

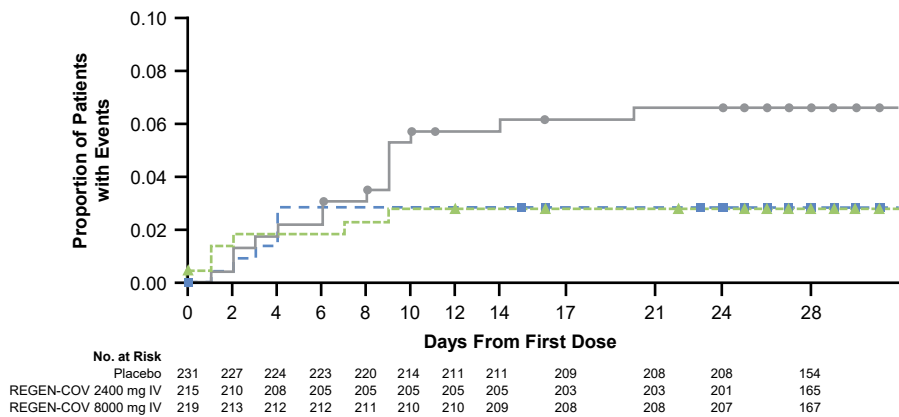
C. Viral Load over Time According to Baseline Viral Load Category



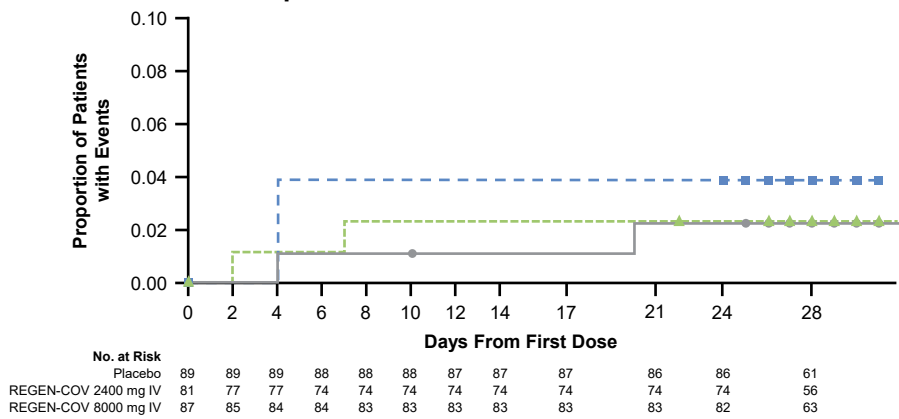
The lower limit of detection (dashed line) is 714 copies per milliliter (2.85 log₁₀ copies per milliliter).
 IV, intravenous(y); SE, standard error.

Figure 2. Proportion of Patients with Covid-19-related MAVs

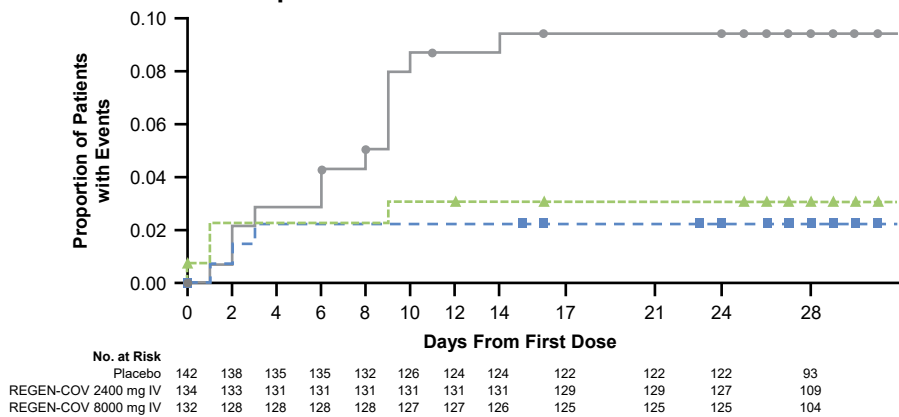
A. Overall (mFAS)



B. No Risk Factor for Hospitalization



C. ≥1 Risk Factor for Hospitalization



—●— Placebo —■— REGEN-COV 2400 mg IV —▲— REGEN-COV 8000 mg IV