REGN-COV2, a Neutralizing Antibody Cocktail [casirivimab and imdevimab], in Outpatients with Covid-19 Weinreich DM et all

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Background

- In an ongoing trial, authors were investigating REGN-COV2, an antibody cocktail containing two SARS-CoV-2-neutralizing antibodies, in non-hospitalized patients with Covid-19.

- The central hypothesis is that complications and death from Covid-19 emanate from the SARS-CoV-2 viral burden and that reducing this burden should lead to clinical benefit.

- REGN-COV2 is a cock-tail made up of two noncompeting, neutralizing human IgG1 antibodies that target the receptor-binding domain of the SARS-CoV-2 spike protein, thereby preventing viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor.

- Authors prospectively pursued a "cocktail" approach because of previous experience with the emergence of treatment-resistant mutant virus when a single antibody, suptavumab, was used to target respiratory syncytial virus.

- Preclinical studies confirmed that the REGN-COV2 cocktail protects against the rapid emergence of such mutants seen with either single antibody.

- In vivo studies in nonhuman primates have shown profound antiviral activity of REGN-COV2 in reducing viral load when given in a prophylactic context and in improving viral clearance when given in a therapeutic context.

Background

- Authors further hypothesized that in an outpatient context, patients would present at various stages of development of their own native humoral immune response and that exogenously provided antibodies would have the most benefit in patients whose immune response had not yet been initiated.

- Consequently, all patients were screened for the presence of preexisting antibodies against SARS-CoV-2 and were classified as either serum antibody-positive or serum antibody-negative at trial entry.

Methods

- Trial Design: It was an ongoing operationally seam-less (continual enrollment), multicenter, randomized, double-blind, placebo-controlled, phase 1-3 clinical trial involving symptomatic, nonhospitalized patients with Covid-19.

- The interim analysis described here involved the first 275 patients enrolled during the phase 1-2 portion of the trial and was conducted to assess the safety and efficacy of REGN-COV2, to gain an understanding of the natural history of Covid-19 in outpatients, and to refine the end points for subsequent analyses.

- The trial continues to recruit beyond the first 275 patients for whom data are described in this report; the results for the key primary and secondary prespecified end points are planned to be reported at trial completion.

- The data cutoff for this interim analysis was September 4, 2020

- In the phase 1-2 portion of the trial reported here, all patients were randomly assigned (1:1:1) to receive placebo, REGN-COV2 at a dose of 2.4 g (low dose), or REGN-COV2 at a dose of 8.0 g (high dose).

- Each of the two antibodies that make up REGN-COV2 — casirivimab (REGN10933) and imdevimab (REGN10987) — is given in equal doses in the cocktail.

- Details of the randomization stratification are provided in the Supplementary Appendix.

- The phase 1 portion of the trial included additional pharmacokinetic analyses but was otherwise identical to the phase 2 portion.

- The population of patients in the current analysis was pooled from both phases.

Patients

- To be eligible for participation, patients had to be 18 years of age or older and nonhospitalized.

- All patients had to have a confirmed SARS-CoV-2 infection, with a SARS-CoV-2-positive test result received no more than 72 hours before randomization and symptom onset no more than 7 days before randomization.

- An assay for anti-SARS-CoV-2 antibodies was performed in all patients. Because these results were not available at randomization, patients underwent randomization regardless of their baseline serologic status, and the analyses were prespecified to first evaluate efficacy in the sub-group of patients who were serum antibody negative — that is, those patients who tested negative for all three of the following antibod-ies: IgA anti-S1 domain of spike protein, IgG anti-S1 domain of spike protein, and IgG anti-nucleocapsid protein.

- Patients who were positive for any one of these antibodies were designated as serum antibody-positive. A small number of patients could not be evaluated or had borderline results (unknown serum antibody status); analy-ses involving these patients were conducted but are not reported here.

Intervention and Assessments

- At baseline (day 1), REGN-COV2 (at the high dose or low dose) or saline placebo was administered intravenously in a 250-ml normal saline solution over a period of 1 hour.

- The schedule of assessments is described in the protocol, along with a summary of protocol amendments.

- Quantitative virologic analysis, SARS-CoV-2 serum antibody testing, and measurement of the two components of REGN-COV2 in serum are described in the Supplementary Appendix.

End Points

- Multiple prespecified end points were designated for the phase 1-2 portion of the trial However, because of the lack of a prior information that would allow us to correctly select end points, and because certain employees of Regeneron Pharmaceuticals (who had no role in the conduct of the trial) had access to un-blinded early data from the trial as described in the protocol, no formal hypothesis testing was performed.

- The prespecified key virologic end point in the statistical analysis plan was defined as the time-weighted average change in the viral load (in $\log_{10}$ copies per milliliter) from baseline (day 1) through day 7, as measured by quantitative reverse-transcriptase-polymerase-chain-reaction (RT-PCR) testing of nasopharyngeal swab samples obtained from serum antibody-negative patients.

- The change in viral load from baseline to various days during the trial was an additional prespecified virologic end point, and the change in absolute viral load (measured in copies per milliliter) was a post hoc virologic end point.

End Points

- The prespecified key clinical end point was the percentage of patients with at least one Covid-19-related medically attended visit through day 29 in both the serum antibody-negative subgroup and the overall trial population.

- Medically attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalization.

- For assessments of safety, authors collected data on adverse events that occurred or worsened during the observation period (grade 3 and 4; phase 1 only), serious adverse events that occurred or worsened during the observation period (phases 1 and 2), and the following adverse events of special interest (phases 1 and 2): grade 2 or higher hypersensitivity or infusion-related reactions.

- Pharmacokinetic variables included the concentrations of casirivimab and imdevimab in serum over time.

Trial Oversight

- Regeneron designed the trial; gathered the data, together with the trial investigators; and analyzed the data. Regeneron and the authors vouch for the accuracy and completeness of the data, and Regeneron vouches for the fidelity of the trial to the protocol.

- The authors provided critical feedback and final approval of the manu-script for submission. No one who is not an author contributed to writing the manuscript.

- All the investigators had confidentiality agreements with Regeneron.The investigators, site personnel, and Regeneron employees who were involved in collecting and analyzing data were unaware of the treatment-group assignments.

- An independent data and safety monitoring committee periodically monitored unblinded data to make recommendations about trial modification and termination.

- The independent committee and, separately, Regeneron physicians who were aware of the treatment-group assignments and were not involved in the conduct of the trial performed in-
terim data reviews for adapting the trial design.

- 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 the patients provided written informed consent before participating in the trial.

Statistical Analysis

- The statistical analysis plan for the presented analysis was finalized before database lock and unblinding. The full analysis set included the first 275 patients with Covid-19 symptoms who underwent randomization in the combined phase 1-2 portions of the trial.

- A sample of 275 patients (72 in phase 1 and 203 in phase 2) was considered sufficient for the assessment of virologic efficacy, clinical trends, and safety for the purpose of informing subsequent analyses. Because patients could enroll if they had tested positive for SARS-CoV-2 no more than 72 hours before randomization, patients who tested negative by qualitative RT-PCR at baseline (lower limit of detection, 714 copies per milliliter [$2.85\ \log_{10}$ copies per milliliter]) were excluded from analyses of virologic end points in a modified full analysis set.

- Because of the prior hypothesis that patients whose immune system was already clearing the virus were unlikely to benefit from additional antibody therapy, analyses were prespecified in the statistical analysis plan to focus on the serum antibody-negative sub-group. All patients who received REGN-COV2 or placebo were included in the safety population.

- The time-weighted average change from base-line (day 1) through day 7 was calculated for each patient as the area under the concentration-time curve, with the use of the linear trapezoidal rule for change from baseline divided by the time interval of the observation period.

- This end point was analyzed with an analysis-of-covariance model with treatment group, risk factor, and baseline serum antibody status as fixed effects and baseline viral load and treatment group-by-baseline viral load as covariates.

- Confidence intervals in this report were not adjusted for multiplicity. Statistical analyses were performed with SAS software, version 9.4 or higher (SASInstitute).

Results

- Baseline Characteristics

- Of the 275 patients who underwent randomization between June 16, 2020, and August 13, 2020, a total of 269 received REGN-COV2 or placebo. Among the 275 patients, 90 were as-signed to receive high-dose REGN-COV2, 92 to receive low-dose REGN-COV2, and 93 to receive placebo (Fig. 1).

- The median age of the patients in the trial was 44.0 years, 49% were male, 13% identified as Black or African American, and 56% identified as Hispanic or Latino (Table 1).

- The median number of days of reported Covid-19-related symptoms before randomization was 3.0.

- At randomization, 30 of 275 patients (11%) tested negative for SARS-CoV-2 by qualitative RT-PCR and 17 of 275 (6%) tested positive for SARS-CoV-2 but did not have baseline viral load data; therefore, 228 of the 275 patients (83%) who underwent randomization made up the modified full analysis set (i.e., those patients who were confirmed SARS-CoV-2-positive by RT-PCR at baseline).

- At baseline, 123 patients (45%) were serum antibody-positive, 113 (41%) were serum antibody-negative, and 39 (14%) had unknown antibody status. Baseline characteristics according to serum antibody status are shown in Table S1.
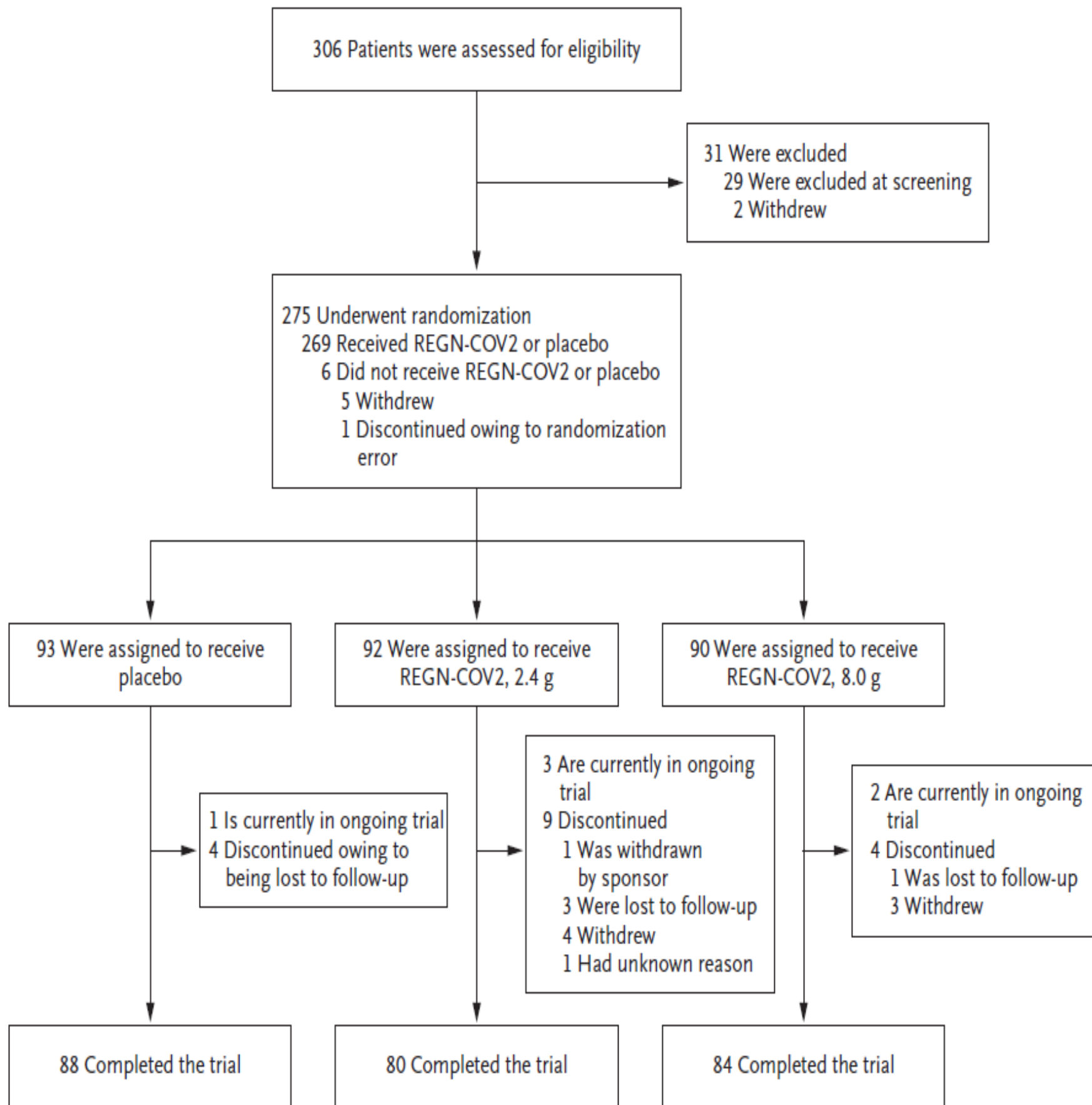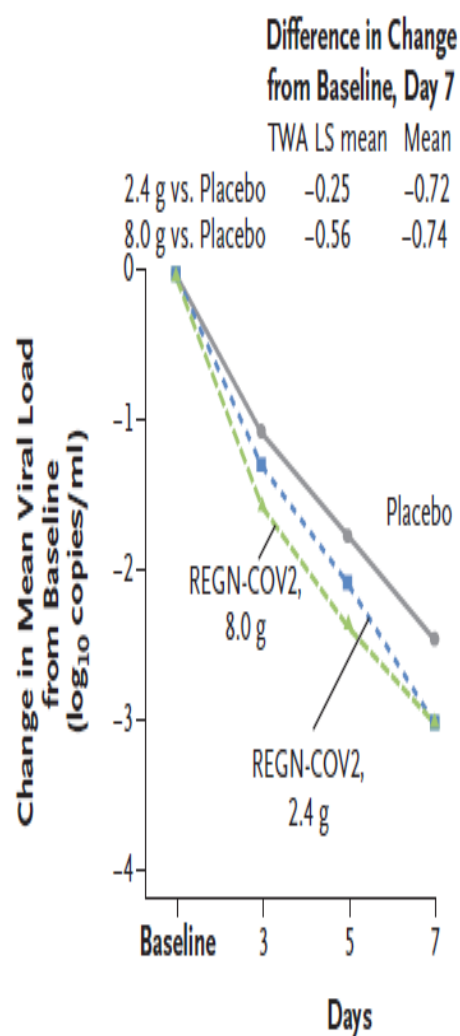
Natural History

- Any treatment effect of REGN-COV2 can be properly interpreted only in the context of an understanding of the endogenous immune response and its effect on viral load and disease course.

- Therefore, in addition to the prespecified trial end points, a major focus of the trial is to examine the natural history of Covid-19.

- The median and mean baseline viral loads were 7.18 $\log_{10}$ copies per milliliter and 6.60 $\log_{10}$ copies per milliliter, respectively, among serum antibody-negative patients and were 3.49 $\log_{10}$ copies per milliliter and 3.30 $\log_{10}$ copies per milliliter, respectively, among serum antibody-positive patients (Fig. S2).

- The raw median baseline viral load among serum antibody-negative patients was also higher than that among serum antibody-positive patients (1.5×10^7 copies per milliliter vs. 3.1×10^3 copies per milliliter). In a retrospective analysis, the presence and titer of neutralizing antibodies were also associated with viral load: serum antibody-positive patients who lacked neutralizing activity had a viral load range similar to that among serum antibody-negative patients.

- Of the 6 patients in the placebo group who had a medically attended visit for worsening Cov-id-19 symptoms, only 1 was from the serum antibody-positive subgroup (1 of 47 [2%]), as compared with 5 from the serum antibody-negative subgroup (5 of 33 [15%]) (Table 2).

- By these measures, patients in the serum antibody-positive subgroup had substantially lower viral loads and a lower likelihood of having a medically attended visit than patients in the serum antibody-negative subgroup.

Virologic Efficacy

- The prespecified key virologic end point was the time-weighted average change from baseline in viral load through day 7 ($\log_{10}$ scale) in patients in the modified full analysis set who were serum antibody-negative at baseline.

- In this group, the least-squares mean difference from placebo was –0.52 $\log_{10}$ copies per milliliter (95% confidence interval [CI], –1.04 to 0.00) in the low-dose REGN-COV2 group, –0.60 $\log_{10}$ copies per mil-liliter (95% CI, –1.12 to –0.08) in the high-dose REGN-COV2 group, and –0.56 $\log_{10}$ copies per milliliter (95% CI, –1.02 to –0.11) in the combined REGN-COV2 group (Table 2).

- In the overall trial population, the least-squares mean differences from placebo were –0.25 $\log_{10}$ copies per milliliter (95% CI, –0.60 to 0.10), –0.56 $\log_{10}$ copies per milliliter (95% CI, –0.91 to –0.21), and –0.41 $\log_{10}$ copies per milliliter (95% CI, –0.71 to –0.10), respectively.

- Additional, post hoc virologic end points included viral load over time and virologic outcomes according to baseline viral load ($>10^4$, $>10^5$, $>10^6$, or $>10^7$ copies per milliliter) and according to baseline serum antibody status (Fig. 2, Figs. S3 through S5, and Table S

- Similar treatment benefits were observed in the covariate-adjusted (prespecified) and unadjusted (post hoc) analyses (Fig. S4). Patients with the highest viral loads had the largest treatment benefit.

- In an analysis on a $\log_{10}$ scale involving patients whose baseline viral load was higher than 10^7 copies per milliliter, the mean reduction in viral load at day 7 was approximately 2-log greater among patients who received REGN-COV2 than among patients who received placebo (Fig. 2). Most of the reduction in viral load was evident by trial day 3 (2 days after infusion).

A Viral Load over Time in the Overall Population

B Viral Load over Time According to Baseline Antibody Status

Serum Antibody–Negative

Serum Antibody–Positive

Difference in Change
from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	−0.25	−0.72
8.0 g vs. Placebo	−0.56	−0.74

Difference in Change
from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	−0.52	−0.59
8.0 g vs. Placebo	−0.60	−0.71

Difference in Change
from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	0.00	−0.45
8.0 g vs. Placebo	−0.39	+0.04

No. at Risk

Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

No. at Risk

Placebo	30	23	28	28	38	35	37	37
REGN-COV2, 2.4 g	35	32	34	34	27	26	27	27
REGN-COV2, 8.0 g	36	34	35	35	29	38	29	29

C Viral Load over Time According to Baseline Viral Load Category

>10^4 copies/ml

Difference in Change from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	−0.36	−0.64
8.0 g vs. Placebo	−0.59	−0.90

Placebo (N=56)
REGN-COV2, 2.4 g (N=60)
REGN-COV2, 8.0 g (N=54)

Mean Viral Load (log$_{10}$ copies/ml)

Baseline 3 5 7

Days

>10^5 copies/ml

Difference in Change from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	−0.59	−0.83
8.0 g vs. Placebo	−0.75	−1.12

Placebo (N=41)
REGN-COV2, 2.4 g (N=52)
REGN-COV2, 8.0 g (N=45)

Baseline 3 5 7

Days

>10^6 copies/ml

Difference in Change from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	−0.81	−1.46
8.0 g vs. Placebo	−1.14	−1.54

Placebo (N=27)
REGN-COV2, 2.4 g (N=34)
REGN-COV2, 8.0 g (N=34)

Baseline 3 5 7

Days

>10^7 copies/ml

Difference in Change from Baseline, Day 7

	TWA LS mean	Mean
2.4 g vs. Placebo	−1.03	−1.84
8.0 g vs. Placebo	−1.32	−1.75

Placebo (N=22)
REGN-COV2, 2.4 g (N=21)
REGN-COV2, 8.0 g (N=28)

Baseline 3 5 7

Days

Clinical Efficacy

- The key prespecified clinical end point was the percentage of patients with one or more medically attended visits.

- In the full analysis set, 6 of 93 patients (6%) in the placebo group and 6 of 182 patients (3%) in the combined REGN-COV2 group had a medically attended visit, a relative difference of approximately 49% (absolute difference vs. placebo, −3 percentage points; 95% CI, −16 to 9).

- In the serum antibody-negative subgroup, 5 of 33 patients (15%) in the placebo group and 5 of 80 patients (6%) in the combined REGN-COV2 group had a medically attended visit, a relative difference of approximately 59% (absolute difference vs. placebo, −9 percentage points; 95% CI, −29 to 11) (Table 2).

Safety

- In this interim analysis, both REGN-COV2 doses (2.4 g and 8.0 g) were associated with few and mainly low-grade toxic effects (Table 3 and Table S3). Among the 269 patients in the safety population, the incidence of serious adverse events and adverse events of special interest that occurred or worsened during the observation period, which included grade 2 or higher infusion-related reactions and hypersensitivity reactions, were balanced between the combined REGN-COV2 dose groups and the placebo group.

- An adverse event of special interest was reported in 2 of 93 patients (2%) in the placebo group and in 2 of 176 patients (1%) in the combined REGN-COV2 dose groups.

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

Event	REGN-COV2			Placebo (N=93)
	2.4 g (N=88)	8.0 g (N=88)	Combined (N=176)	
	number of patients (percent)			
Any serious adverse event	1 (1)	0	1 (1)	2 (2)
Any adverse event of special interest*	0	2 (2)	2 (1)	2 (2)
Any serious adverse event of special interest*	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days	0	2 (2)	2 (1)	1 (1)
Grade ≥2 hypersensitivity reaction within 29 days	0	1 (1)	1 (1)	2 (2)
Adverse events that occurred or worsened during the observation period†				
Grade 3 or 4 event	1 (1)	0	1 (1)	1 (1)
Event that led to death	0	0	0	0
Event that led to withdrawal from the trial	0	0	0	0
Event that led to infusion interruption*	0	1 (1)	1 (1)	1 (1)

* 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 REGN-COV2 or placebo to the last study visit.

Pharmacokinetics

- The mean and individual concentration-time profiles for the components of REGN-COV2 — casirivimab and imdevimab — increased in a dose-proportional manner and were consistent with linear pharmacokinetics for single intravenous doses (Figs. S6 and S7).

- The mean (±SD) day 29 concentrations of casirivimab and imdevimab in serum were 68.0±45.2 mg per liter and 64.9±53.9 mg per liter, respectively, for the low (1.2 g) doses and 219±69.0 and 181±64.9 mg per liter, respectively, for the high (4.0 g) doses (Table S4);

- The mean estimated half-life ranged from 25 to 37 days for both antibodies (Table S5).

Discussion

- To test the hypothesis that exogenously provided antibodies would have the most benefit in patients whose own immune response had not yet been initiated, our trial first characterized the natural history of Covid-19 and showed that, in the outpatient context, preexisting antibodies against SARS-CoV-2 were associated with lower viral loads at baseline and a potential lower likelihood of future medically attended visits.

- One possible reason for this observation is that patients whose endogenous immune responses were active (serum antibody-positive) were already efficiently clearing the virus, as compared with patients whose immune response had not yet been initiated (serum antibody-negative).

- These findings are consistent with those in other studies that have shown an association between native antibodies against SARS-CoV-2 and viral loads.

- Overall, the findings are consistent with the hypothesis that most infected persons successfully recover because of their endogenous immune response.

- This understanding of the natural history of Covid-19 supported our prospective hypothesis that an exogenously provided antibody cocktail would have the most benefit in patients whose own immune response had not yet been initiated, since such patients would have higher baseline viral loads and a higher likelihood of seeking additional medical treatment.

- Our data indicate that REGN-COV2 enhanced clearance of virus, particularly in patients in whom an endogenous immune response had not yet been initiated (i.e., serum antibody-negative) or who had a high viral load at baseline.

- A possible difference in the percentage of patients with medically attended visits was observed between the combined REGN-COV2 dose groups and the placebo group (difference, −3 percentage points; 95% CI, −16 to 9), and this effect was also driven almost entirely by patients who were serum antibody-negative at baseline (difference, −9 percentage points; 95% CI, −29 to 11).

- As hypothesized, in patients whose immune response was active at trial entry, the potential to improve this response with an exogenous antibody cocktail was minimal. Administration of such a cocktail did not increase the viral load and therefore did not appear to impede ongoing antiviral activity.

- In this regard, it may be useful to evaluate the potential for REGN-COV2 to affect long-term immunity to SARS-CoV-2, regardless of patients' serum antibody status.

- Higher viral loads have been correlated with an increased risk of death among hospitalized patients.[22] High-titer convalescent-phase plasma may lower the SARS-CoV-2 viral load and thereby reduce the risk of death from Covid-19.

- Like-wise, in this trial, clearance of the virus was correlated with better clinical outcomes. The neutralizing titers achieved with REGN-COV2 were more than 1000 times the titers achievable with convalescent-phase plasma, and REGN-COV2 had a profound and rapid effect on viral load, with most reduction occurring within 48 hours.

- This was striking even in the patients with the highest quantifiable viral loads, greater than 10^7 copies per milliliter; these patients were presumably at the highest risk for additional complications and death.

- Our results also suggest a testable hypothesis that a shorter time to elimination of viral load would reduce the time of potential infectivity. This hypothesis is being studied in a separate REGN-COV2 trial.

Discussion

- The safety of REGN-COV2 was as expected for a fully human antibody against an exogenous target. A low incidence of serious adverse events that occurred or worsened during the observation period and of infusion-related or hypersen-
sitivity reactions was observed.

- The pharmacokinetics of each antibody were linear and dose-proportional. Although antidrug-antibody results are not available, no patient had a concentration-time profile in serum that was consistent with altered elimination due to the development of antidrug antibodies.

- For more than 95% of patients, concentrations of the drug in serum at day 29 were well above the predicted neutralization target concentration based on in vitro and preclinical data. This long half-life of REGN-COV2 suggests that treatment could result in long-term passive immunity for several months. The pharmacokinetic data were similar at each dose of REGN-COV2.

- An important limitation of this interim portion of our trial is that, although the analyses according to antibody status were prespecified, no formal hypothesis testing was performed to control type I error; in addition, the analyses according to baseline viral load were post hoc.

- These results should therefore be rigorously tested in the next analysis in this ongoing trial.

Discussion

- Similar findings showing a reduction in viral load and potential improvement in clinical outcomes were independently reported with a single neutralizing antibody against SARS-CoV-2.

- It was recently shown that an antibody cocktail approach provided a profound survival benefit for patients infected with Ebola virus.

- This study results suggests that an antibody cocktail against SARS-CoV-2 can also be an effective antiviral therapy, enhancing viral clearance and thus leading to improved outcomes, particularly in patients whose own immune response to the virus is slow to initiate.

- Further studies, including the continuing phase 3 portion of this trial, are needed to confirm these effects.

THANK YOU