Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2035002

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

SUPPLEMENTARY APPENDIX

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Study Sites and Investigators

AGA Clinical Trials, Hialeah, FL: Dario Altamirano, Ximena Graber, Dickson Ellington

Arizona Liver Health, Tucson, AZ: Anita Kohli, Vicki McIntyre, Yessica Sachdeva

Arizona Liver Health, Chandler, AZ: Yessica Sachdeva, Anita Kohli

Baylor University Medical Center, Dallas, TX: Mezgebe Berhe, Haley Clinton, Uriel Sandkovsky, Emma Dishner, Rahaf Al Masri, Erin Duhaime

Clinical Research of Central Florida, Winter Haven, FL: Robinson Koilpillai, Stephanie Cassady, Jennifer Cox, Eduardo Torres

Florida Pulmonary Research Institute, LLC, Winter Park, FL: Faisal A. Fakih, Faisal M. Fakih, Fernando Alvarado, Daniel Layish, Jose Diaz

FOMAT Medical Research, Oxnard, CA: Augusto Focil, Griselda Rosas, Stevan Correa, Michael Bogseth

Global Clinical Professionals Research, Saint Petersburg, FL: Roxana Stoici, Gualberto Perez, Joseph Pica, Enrique Villareal

Holy Name Medical Center, Teaneck, NJ: Suraj Saggar, Thomas Birch, Benjamin De La Rosa, Karyna Neyra, Erina Kunwar

IACT Health, Columbus, GA: Jeffrey Kingsley, April Pixler

Medical University of South Carolina, Charleston, SC: Eric Meissner, Andrew Goodwin, Deeksha Jandhyala, Nandita Nadig

Midland Florida Clinical Research Center, Deland, FL: Godson Oguchi, DeAndrea Duffus

Midway Immunology and Research Center, Fort Pierce, FL: Moti Ramgopal, Brenda Jacobs, Lisa Cason, Angela Trodglen

Next Level Urgent Care, Houston, TX: Terence Chang, Robbyn Traylor, Lenee Gordon, John McDivitt

PMG Research of McFarland Clinic, Ames, IA: Jennifer Killion, Rupal Amin, Shauna Basener, Timothy Lowry

PMG Research of Wilmington, Wilmington, NC: Kevin Cannon, Mesha Chadwick

Queens NYC Health + Hospitals, Jamaica, NY: Jazila Mantis, Margaret Kemeny, Merjona Saliaj

Remington Davis, Columbus, OH: Edward Cordasco, Brian Zeno, Heather Holmes

Sarasota Memorial Hospital, Sarasota, FL: Manuel Gordillo, Rishi Bhattacharyya, Sudha Tallapragada, Annette Artau, Julie Larkin, Roberto Mercado, Michael Milam, Natan Kraitman, Sarah Temple, Lenka Offner, Rabih Loutfi, Kirk Voelker, Michael Lowry

Sun Research Institute, San Antonio, TX: Carl Dukes, Robert Bass, Larry Lothringer, Leonel Reyes

Tandem Clinical Research, Marrero, LA: Adil Fatakia, Marissa Miller, Kristen Clinton, Gary Reiss

The George Washington University Hospital, Washington, DC: David Diemert, Afsoon Roberts, David Parenti, Hana Akselrod, Marc Siegel, Andrew Meltzer, Elissa Malkin

The University of Texas Health Science Center, Tyler, TX: Julie Philley, Megan Devine, Richard Yates, Steven Hickerson

Triple O Research Institute PA, West Palm Beach, FL: Olayemi Osiyemi, Jose A. Menajovsky-Chaves, Christina Campbell

Universal Medical and Research Center, LLC, Miami, FL: Gerard Acloque**,** Agustin Martinez

University of Colorado, Aurora, CO: Thomas Campbell, Martin Krsak, Steven Johnson, Hillary Dunlevy

Willis-Knighton Physician Network, Shreveport, LA: Joseph Bocchini, Clint Wilson

Regeneron Study Team

Achint Chani, Adebiyi Adepoju, Adnan Mahmood, Aisha Mortagy, Ajla Dupljak, Alison Brown, Alpana Waldron, Amanda Cook, Amy Froment, Andrea Hooper, Andrea Margiotta, Andrew Bombardier, Anne Smith, Aswani Bathula, Bari Kowal, Barry Siliverstein, Benjamin Horel, Bret Musser, Brian Bush, Brian Head, Bryan Zhu, Camille Debray, Careta Phillips, Carol Lee, Caryn Trbovic, Catherine Elliott, Chad Fish, Charlie Ni, Charlotte Lyon, Christina Perry, Christine Enciso, Christopher Caira, Christopher Chamak, Christopher Powell, Cliff Baum, Colby Burk, Cynthia Pan, David Liu, David Stein, Daya Gulabani, Deborah Leonard, Denise Bonhomme, Denise Kennedy, Derrick Bramble, Dhanalakshmi Barron, Diana Rofail, Dipinder Kaur, Dona Bianco, Donna Gambaccini, Eduardo Forleo Neto, Edward Jean-Baptiste, Ehsan Bukhari, Elizabeth Bucknam, Emily Nanna, Esther Huffman O'Keefe, Evelyn Gasparino, Georgia Bellingham, Giane Sumner, Grainne Moggan, Grainne Power, Haitao Gao, Haixia Zeng, Heath Gonzalez, Helen Kang, Hibo Noor, Ian Minns, James Donohue, Janice Austin, Janie Parrino, Jeannie Yo, Jenna McDonnell, Jennifer Hamilton, Jessica Boarder, Jing Xiao, Jingchun Yu, Joanne Malia, Joanne Tucciarone, John Strein, Jonathan Cohen, Jordan Ursino, Joseph Im, Joseph Wolken, Karen Browning, Karen Yau, Kenneth Turner, Kimberly Dornheim, Kit Chiu, Kristina McGuire, Kristy Macci, Kurt Ringleben, Kyle Foster, Lacey Douthat, Latora Knighton, Lisa Boersma, Lisa Hersh, Lisa Purcell, Lisa Sherpinsky, Lori Geissler, Marc Dickens, Marco Mancini, Martha Simpkins, Meagan O'Brien, Michael Batchelder, Michael Partridge, Michal Rozanski, Michel Tarabocchia, Michelle Wong, Mivianisse Rodriguez, Moetaz Albizem, Muriel O'Byrne, Nagendher Burra, Neena Sarkar, Nicholas Moore, Nicole Memblatt, Nikki Miocevic,

Nirav Shah, Nitin Kumar, Olga Herrera, Patrick Floody, Paul D'Ambrosio, Qin Li, Rafia Bhore, Rakiyya Ali, Ramya Iyer, Ravikanth Chava, Rinol Alaj, Romana Hosain, Ruchin Gorawala, Ryan Yu, Rylee Fogarty, S. Balachandra Dass, Sagarika Bollini, Samit Ganguly, Sandra DeCicco, Sara Dale, Sara Hamon, Sarah Cassimaty, Selin Somersan-Karakaya, Shane McCarthy, Sharon Henkel, Shazia Ali, Soraya Nossoughi, Steven Elkin, Sumathi Sivapalasingam, Susan Irvin, Tami Min, Ted Burczynski, Theresa Devins, Thomas Norton, Travis Bernardo, Vinh Nuce, Wilson Caldwell, Yanmei Tian, Yasmin Khan

Supplementary Methods

Randomization Stratification

In the Phase 2 study, randomization was stratified by:

- Presence/absence of coronavirus disease 2019 (Covid-19) symptoms (i.e., symptomatic versus asymptomatic cohort)
- Country
- Risk factors for hospitalization due to Covid-19 (no risk factors for hospitalization due to Covid-19 versus ≥1 risk factor for hospitalization due to Covid-19)

The following are considered risk factors for the purposes of stratification:

- Age >50 years
- Obesity, defined as body mass index >30
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Chronic metabolic disease, including diabetes
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on investigator's assessment (examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, poorly controlled human immunodeficiency virus [HIV] or acquired immunodeficiency syndrome [AIDS], and prolonged use of immune-weakening medications)

Inclusion and Exclusion Criteria

Inclusion criteria:

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Is male or female ≥18 years of age (or country's legal age of adulthood) at randomization
2. Has severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, reverse transcription polymerase chain reaction [RT-PCR], or other molecular diagnostic assay, using an appropriate sample such as nasopharyngeal, nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization. A historical record of positive result from test conducted ≤72 hours prior to randomization is acceptable.
3. Meets 1 of the following 2 criteria:
    a. **Symptomatic Cohort (all phases):** Has symptoms consistent with Covid-19 as determined by the investigator with onset ≤7 days before randomization

    or

    b. **Asymptomatic Cohort (Phase 2 only)**: Meets all of the following:
        - Has had no symptoms consistent with Covid-19 (as determined by the investigator) occurring at any time <2 months prior to randomization
        - Has had no positive SARS-CoV-2 test results from a sample collected >7 days prior to randomization

- Has had no known contact (of any duration) with an individual who has confirmed Covid-19 or confirmed positive SARS-CoV-2 test result >14 days prior to randomization.

4. Maintains O_2 saturation ≥93% on room air
5. Is willing and able to provide informed consent signed by study patient or legally acceptable representative
6. Is willing and able to comply with study procedures, including providing samples for viral shedding testing

Exclusion criteria:

A patient who meets any of the following criteria will be excluded from the study:

1. Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to Covid-19
2. Has participated, or is participating, in a clinical research study evaluating Covid-19 convalescent plasma, monoclonal antibodies (mAbs) against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
3. Prior, current, or planned future use of any of the following treatments: Covid-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or Covid-19 Emergency Use Authorization approved treatments, where prior use is defined as the past 30 days or less than 5 half-lives of the investigational product (whichever is longer) from screening

4. Has known allergy or hypersensitivity to components of study drug
5. Has been discharged, or is planned to be discharged, to a quarantine center
6. Pregnant or breastfeeding women
7. Continued sexual activity in women of childbearing potential (WOCBP)* or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose.

   Highly effective contraceptive measures in women include:

   - Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening,
   - Intrauterine device (IUD),
   - Intrauterine hormone-releasing system (IUS),
   - Bilateral tubal ligation,
   - Vasectomized partner,† and/or
   - Sexual abstinence.‡,§

   Male study participants with WOCBP partners are required to use condoms unless they are vasectomized† or practice sexual abstinence.‡,§

*WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH)

level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

†Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success.

‡Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

§Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Summary of Protocol Amendments and Study Adaptations

Protocol Version (Date)	Key Study Design Feature or Design Update

Original Protocol (May 29, 2020)	• Phase 1/2/3 master protocol
	• Patients randomized 1:1:1 to a single intravenous dose of 2.4 g REGN-COV2, 8.0 g REGN-COV2, or placebo
	• Phase 1 primary endpoints:
	  ○ Proportion of patients with treatment-emergent serious adverse events through day 29
	  ○ Proportion of patients with infusion-related reactions (grade ≥2) through day 4
	  ○ Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
	  ○ Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to day 22, as measured by quantitative reverse transcription quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal swab samples
	• Phase 2 primary endpoint: Time-weighted average change from baseline in viral shedding (log_{10} copies/ml)

	from day 1 to day 22, as measured by RT-qPCR in saliva samples
Amendment 1 (June 3, 2020)	• Updates to Phase 1 study design for the sentinel safety group
Amendment 2 (June 19, 2020)	• Clarifications to Phase 1 study that grades 3 and 4 treatment-emergent adverse events will be collected • Clarifications and updates to Phase 1 study procedures and objectives, including virology • Adjustments to Phase 1 endpoints related to intensive care unit and mechanical ventilation to ensure consistency with statistical analysis plan • Study sites increased to US and other countries • Country added as a stratification factor for Phase 2 • Clarifications to inclusion criteria added • Study stopping criteria updated
Amendment 3 (July 4, 2020)	• Primary virologic efficacy in Phase 2 assessed using nasopharyngeal swab samples (previously saliva samples); planned Phase 3 secondary virologic endpoints updated accordingly • Additional patients may be enrolled in Phase 1 to replace patients who have missing or negative virologic samples
Amendment 4 (July 11, 2020)	• Nasal swabs and saliva samples no longer collected in Phase 2 or Phase 3 (nasopharyngeal swabs only)

	• Phase 2 sample size increased to enable additional enrollment • Interim analysis plan updated • Modified full analysis set (mFAS) was added to allow adequate assessment of virologic efficacy • Additional secondary virologic endpoint added
Amendment 5 (August 8, 2020)	• Added new cohort of patients in Phase 2 to evaluate asymptomatic patients with SARS-CoV-2 infection; planned enrollment for Phase 2 increased to accommodate this cohort • Added new secondary clinical endpoint in Phase 2 to assess development of symptoms consistent with Covid-19 • Updated inclusion/exclusion criteria to broaden patient eligibility and provide operational flexibility • Additional blood sampling and biomarker assessments added in Phase 2 • Phase 2 interim analysis plan updated to allow flexibility

Analytical Methods of Quantification

Quantitative Virology Assay

Nasopharyngeal swabs were collected in 3 ml Viral Transport Medium (Catalog R99, Hardy's Diagnostics) at baseline (day 1) and study days 3, 5, 7, 9, 11, 15, 18, 22, 25 and 29. Virologic testing for SARS-CoV-2 infection was performed at Viracor Eurofins Clinical Diagnostics (Missouri, USA) by quantitative real-time RT-PCR (RT-qPCR). RNA was extracted from clinical samples with the Applied Biosystems MagMAX™ Viral/Pathogen II MVP II Nucleic Acid Isolation Kit (Catalog A48383, ThermoFisher) on the ThermoFisher KingFisher FLEX. Viral nucleic acids were detected and quantified using a SARS-CoV-2 RT-qPCR Swab assay (Viracor Eurofins Clinical Diagnostics) which is performed using oligonucleotide primers and Taqman probes for the detection of two regions of the viral N protein gene region of SARS-CoV-2 and an internal extraction and amplification control target on ABI 7500 SDS Instruments (Applied Biosystems). Assay data are presented in units of copies of SARS-CoV-2 nucleic acids per ml of Viral Transport Medium (VTM) yielded from the collection of nasopharyngeal swab specimens (copies/ml). The limit of detection was 299 copies/ml (2.47 $\log_{10}$ copies/ml), the lower limit of quantification was 714 copies/ml (2.85 $\log_{10}$ copies/ml), and the upper limit of quantification was 7.1×10^7 copies/ml (7.85 $\log_{10}$ copies/ml). Analysis-positive PCR results below the lower limit of quantification were imputed as half the lower limit of quantification (357 copies/ml) and negative PCR results were imputed as 0 $\log_{10}$ copies/ml (1 copy/ml). PCR results greater than the upper limit of quantification were not imputed.

SARS-CoV-2 Serology Testing

Serum was collected from patients at baseline. The Euroimmun Anti-SARS-CoV-2 ELISA (IgG) and the Euroimmun Anti-SARS-CoV-2 ELISA (IgA) assays were validated and run at ICON Laboratories (Farmingdale, NY) to detect endogenous anti-S1 protein antibodies. In addition, the Abbott Architect SARS-CoV-2 IgG assay was validated and run at ICON Laboratories (Farmingdale, NY) to detect endogenous anti-nucleocapsid antibodies.

Measurement of REGN10933 and REGN10987 in Serum

Concentrations of REGN10933 and REGN10987 in serum were measured using a non-validated, fit for purpose Liquid Chromatography-Multiple Reaction Monitoring Mass Spectrophotometry (LC-MRM-MS) method with a lower limit of quantification of 10 to 25 mg/L. The LC-MRM-MS method is based on the analysis of a unique peptide generated by enzymatic digestion of each monoclonal antibody, so as to allow for each monoclonal antibody to be individually quantitated from the human serum samples collected during the study.

Protocol-defined Prespecified Endpoints for the Phase 1 and 2 Studies

Prespecified endpoints for the Phase 1 and 2 studies are presented for reference only. These endpoints may not have been evaluated in the presented interim analysis. For the specific endpoints analyzed for the first 275 patients reported in this manuscript, please refer to manuscript text and the additional descriptive efficacy endpoints for the presented interim analysis in the next section of the appendix.

Phase 1 primary endpoints:

- Proportion of patients with treatment-emergent serious adverse events (SAEs) through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to day 22, as measured by RT-qPCR in nasopharyngeal swab samples.

Phase 2 primary endpoint:

- Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to day 22, as measured by RT-qPCR in nasopharyngeal swab samples

Phase 1 secondary endpoints:

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (nasopharyngeal swabs, nasal swabs, saliva)
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in nasopharyngeal swabs
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs
- Correlation and concordance of RT-qPCR results across different sample types (nasopharyngeal, nasal, and saliva)
- Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to post-baseline study days (e.g., day 5, 7, 15, and 29)

Clinical

- Proportion of patients with ≥1 Covid-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 Covid-19 related medically-attended visits through day 29
- Total number of Covid-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to Covid-19 by day 29

- Proportion of patients with ≥1 outpatient or telemedicine visit due to Covid-19 by day 29

Pharmacokinetics/anti-drug antibodies

- Concentrations of REGN10933 and REGN10987 in serum and corresponding pharmacokinetic parameters
- Immunogenicity as measured by anti-drug antibodies to REGN10933 and REGN10987

Phase 2 secondary endpoints:

Virologic

- Time to negative RT-qPCR in nasopharyngeal swabs with no subsequent positive RT-qPCR
- Change from baseline in viral shedding at each visit through day 29, as measured by RT-qPCR in nasopharyngeal samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/ml) from day 1 to post-baseline study days (e.g., day 5, 7, 15, and 29)

Clinical

- Proportion of patients with ≥1 Covid-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 Covid-19 related medically-attended visits through day 29
- Total number of Covid-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to Covid-19 by day 29

- Proportion of patients admitted to an intensive care unit (ICU) due to Covid-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to Covid-19 by day 29
- Proportion of patients requiring mechanical ventilation due to Covid-19 by day 29
- Days of hospitalization due to Covid-19
- Proportion of patients with all-cause mortality by day 29
- Time to first onset of symptoms consistent with Covid-19 (asymptomatic cohort only)
- Duration of symptoms consistent with Covid-19
- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Pharmacokinetics/anti-drug antibodies

- Concentrations of REGN10933 and REGN10987 in serum
- Immunogenicity as measured by anti-drug antibodies to REGN10933 and REGN10987

Exploratory endpoints for Phase 1 only:

- Proportion of patients admitted to an ICU due to Covid-19 by day 29
- Proportion of patients requiring mechanical ventilation due to Covid-19 by day 29

Exploratory endpoints for Phase 1 and Phase 2:

- Proportion of patients with treatment failure having mutations in the gene encoding the SARS-CoV-2 S protein through day 29
- Change and percentage change in neutrophil-lymphocyte ratio at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29
- Change and percentage change in C-reactive protein at each visit through day 29
- Change and percentage change in lactate dehydrogenase at each visit through day 29
- Change in Symptom Evolution of Covid-19 (SE-C19) item scores over time
- Change in Patient Global Impression of Severity (PGIS) score over time
- Patient Global Impression of Change (PGIC) score at day 29

Statistical Analysis Plan-Defined Additional Descriptive Efficacy Endpoints for the Presented Interim Analysis

Endpoint	Category	Timepoint	Population
Time-weighted average change from baseline, and percent change in viral load	Virologic	Through each post-baseline timepoint	Seronegative mFAS
Proportion of patients with high viral load (>10^4 copies/ml)	Virologic	At day 9 and at all other timepoints	Overall mFAS Seronegative mFAS
Proportion of patients with low viral load below limit of detection	Virologic	At day 9 and at all other timepoints	Overall mFAS Seronegative mFAS
Proportion of patients with low viral load below lower limit of quantification	Virologic	At day 9 and at all other timepoints	Overall mFAS Seronegative mFAS
Time to sustained negative PCR	Virologic	Through day 15	Overall mFAS Seronegative mFAS
Time-weighted average change from baseline in viral load	Virologic	Through day 7	Overall mFAS Seropositive mFAS
Time-weighted average change from baseline in viral load	Virologic	Through day 11	Overall mFAS Seronegative mFAS
Time to symptom resolution	Symptom	Through day 11	Seronegative FAS
Time to fatigue resolution	Symptom	Through day 11	Seronegative FAS
Time to symptom alleviation (all symptoms)	Symptom	Through day 11	Overall FAS Seronegative FAS
Time to sustained alleviation (all symptoms)	Symptom	Through day 22	Overall FAS Seronegative FAS
Time to sustained resolution (all symptoms)	Symptom	Through day 22	Overall FAS Seronegative FAS
Time to resolution of each individual symptom	Symptom	Through day 22	Overall FAS Seronegative FAS
Percent change in C-reactive protein from baseline	Biomarker	At day 7 (Phase 1 only) At day 29 (Phase 1 / 2)	Overall FAS Seronegative FAS

Additional Statistical and Pharmacokinetic Analysis Methods

Additional Statistical Methods

Continuous endpoints were analyzed using an Analysis of Covariance (ANCOVA) model with treatment group, baseline serum antibody status, and risk factor (0 vs ≥1 risk factors) as fixed effects and baseline viral load as covariate, and continuous longitudinal data were analyzed using a mixed effect model for repeated measures (MMRM) with an additional term of treatment-by-timepoint interaction. Since the correlation between the baseline viral load and post-baseline viral load data were not identical among the three treatment groups, and varied over time, interaction terms for baseline viral load by treatment group and baseline viral load by timepoint (MMRM only) were added to the models after finalization of the statistical analysis plan. In addition, pairwise t-test was used to compare change from baseline viral load between treatment and placebo at each time point without covariate adjustment. Confidence intervals for differences in proportion endpoints were based on exact method. While many of the analyses were prespecified, there was no specific hypothesis testing order to control for Type 1 error. Because the key virologic endpoint was prespecified in seronegative patients and baseline serology was associated with baseline viral load, additional analyses of virologic endpoints by baseline viral load were conducted post-hoc to explain the anti-viral effects in high risk patients.

Missing Data Handling

Missing data for virology endpoints was handled as described in Analytical Methods of Quantification. For categorical variables, patients with missing data were included in calculations of percentages.

Pharmacokinetic Analysis Methods

The pharmacokinetics (PK) analysis population included all patients who received any study drug (safety population) and who had at least 1 non-missing result following the first dose of study drug. Patients were analyzed based on actual treatment received. From Phase 1, 45 patients were included in the PK analysis set, 22 for the 2.4 g dose and 23 for the 8.0 g dose. Overall, the PK analysis set is comprised of 45 patients.

Blood samples for quantification of concentrations of REGN10933 and REGN10987 in serum were collected pre-dose on day 1, within 1 hour after the end of infusion, and on days 3, 5, 7, 15, and 29 post-dose.

From the above drug concentration sampling schedule, PK parameters were determined by non-compartmental methods (Gibaldi 1982); using Phoenix WinNonlin (Certara Corporation). Area Under the Curve (AUC_{0-28}) was determined using the log-linear trapezoidal rule and actual sample collection times (Gibaldi 1982). C_{max} was determined as the maximum observed concentration in serum. The observed half-life was estimated using actual times at the nominal visit days; 15 and 29 for each patient with a negative slope in the concentration-time profile between days 15 and 29 (e.g.

C_{15}>C_{29}). One patient with a negative slope, but a calculated $t_{1/2}$ of 536 days, was considered an outlier and excluded from the reported mean half-life.

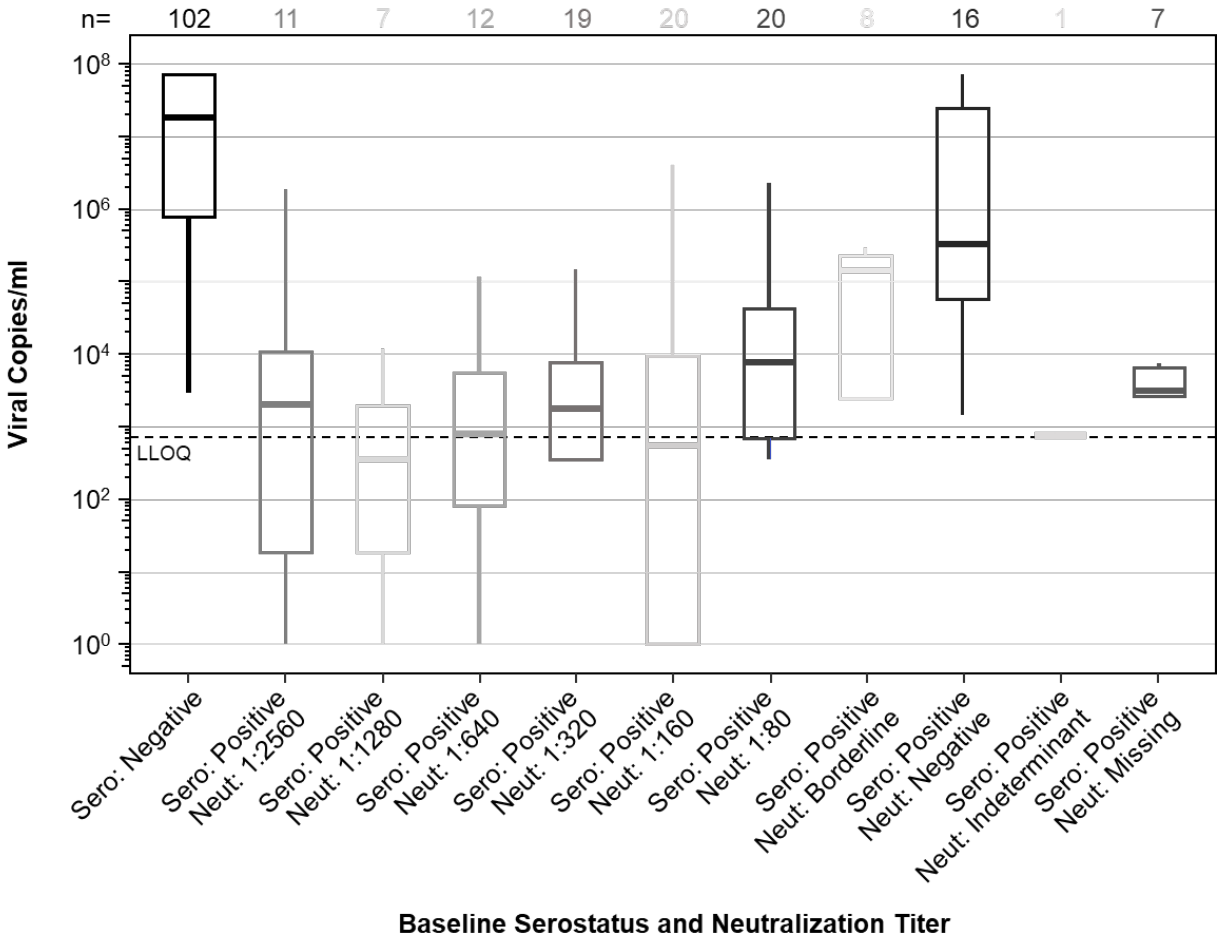
Supplementary Study Results

The Presence and Titer of Baseline Endogenous Anti-SARS-CoV-2 Neutralizing Antibodies is Associated with Baseline Viral Load

To further characterize how effective baseline immune response was, the ability of endogenous antibodies to neutralize SARS-CoV-2 was measured in baseline samples from those COV-2067 patients who tested positive in at least one of the three initial serology assays (Euroimmun IgA, EuroImmun IgG, Abbott Architect IgG) using a pseudovirus neutralization assay[1] (Vyriad,Inc). Shown are the available data from the 275 patients included in the first database lock.

As baseline neutralization titer decreased, a trend for increasing baseline viral load was observed. Patients who had detectable anti-SARS-CoV-2 antibodies lacking neutralization activity had a viral load range more similar to serum antibody–negative patients (Figure below).

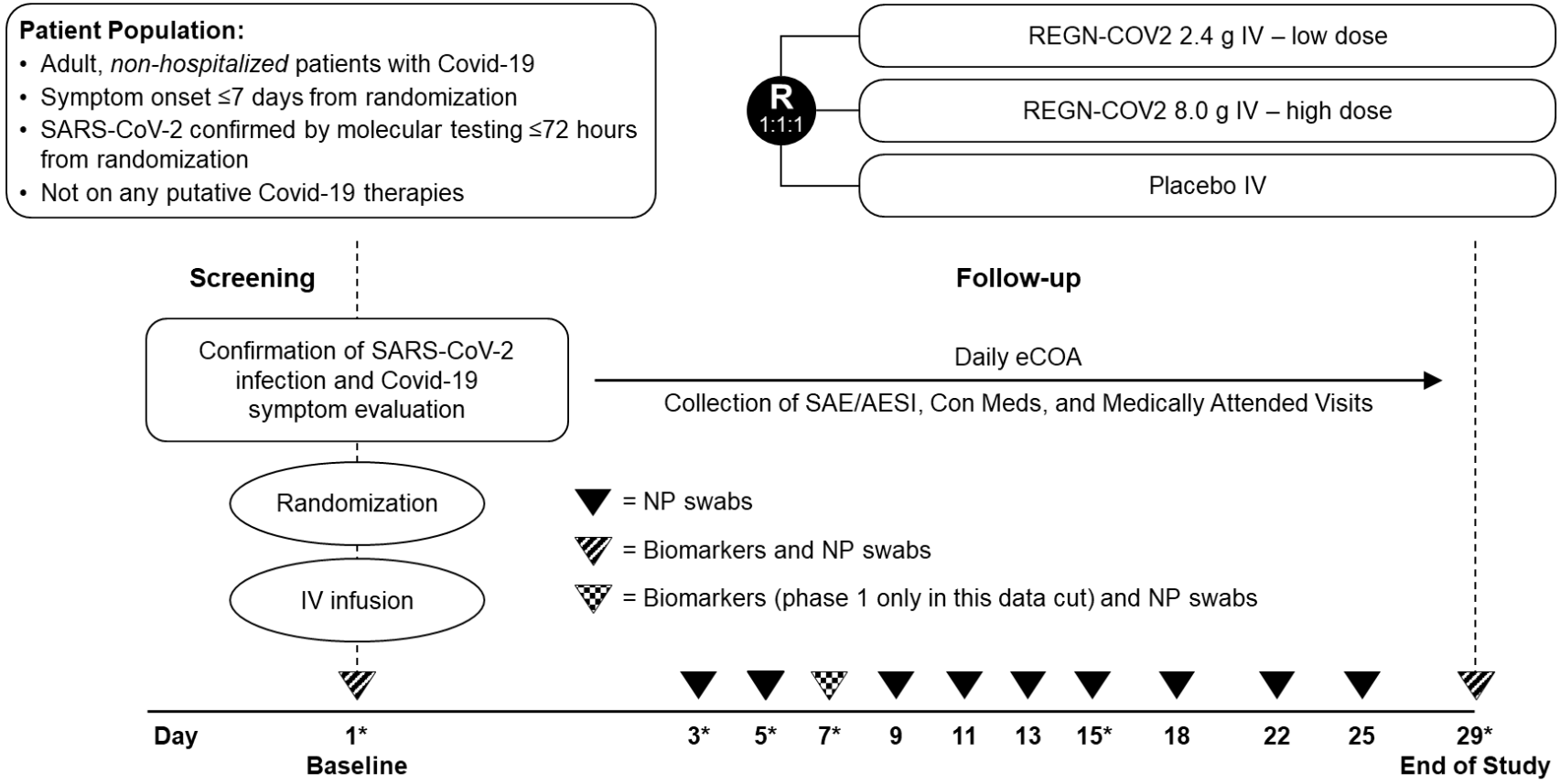
Figure. Baseline Neutralizing Status and Titer of Endogenous anti-SARS-CoV2 Antibodies is Associated with Viral Load (copies/ml).



Sero:negative – negative in all 3 serology assays, not tested for neutralization; Sero: positive/Neut 1:2560 – positive in at least one serology assay, 1:2560 neutralizing titer; Sero: positive/Neut 1:1280 – positive in at least one serology assay, 1:1280 neutralizing titer; Sero:positive/Neut 1:640 – positive in at least one serology assay, 1:640 neutralizing titer; Sero:positive/Neut 1:320 – positive in at least one serology assay, 1:320 neutralizing titer; Sero:positive/Neut 1:160 – positive in at least one serology assay, 1:160 neutralizing titer; Sero:positive/Neut 1:80 – positive in at least one serology assay, 1:80 neutralizing titer; Sero:positive/Neut borderline – positive in at least one serology assay, borderline positive neutralization assay result; Sero:positive/Neut Negative – positive in at least one serology assay, negative neutralizing result; Sero:positive/Neut Indeterminant – positive in at least one serology assay, discordant duplicate neutralization results; Sero:positive/Neut Missing – positive in at least one serology assay, no neutralization data available.

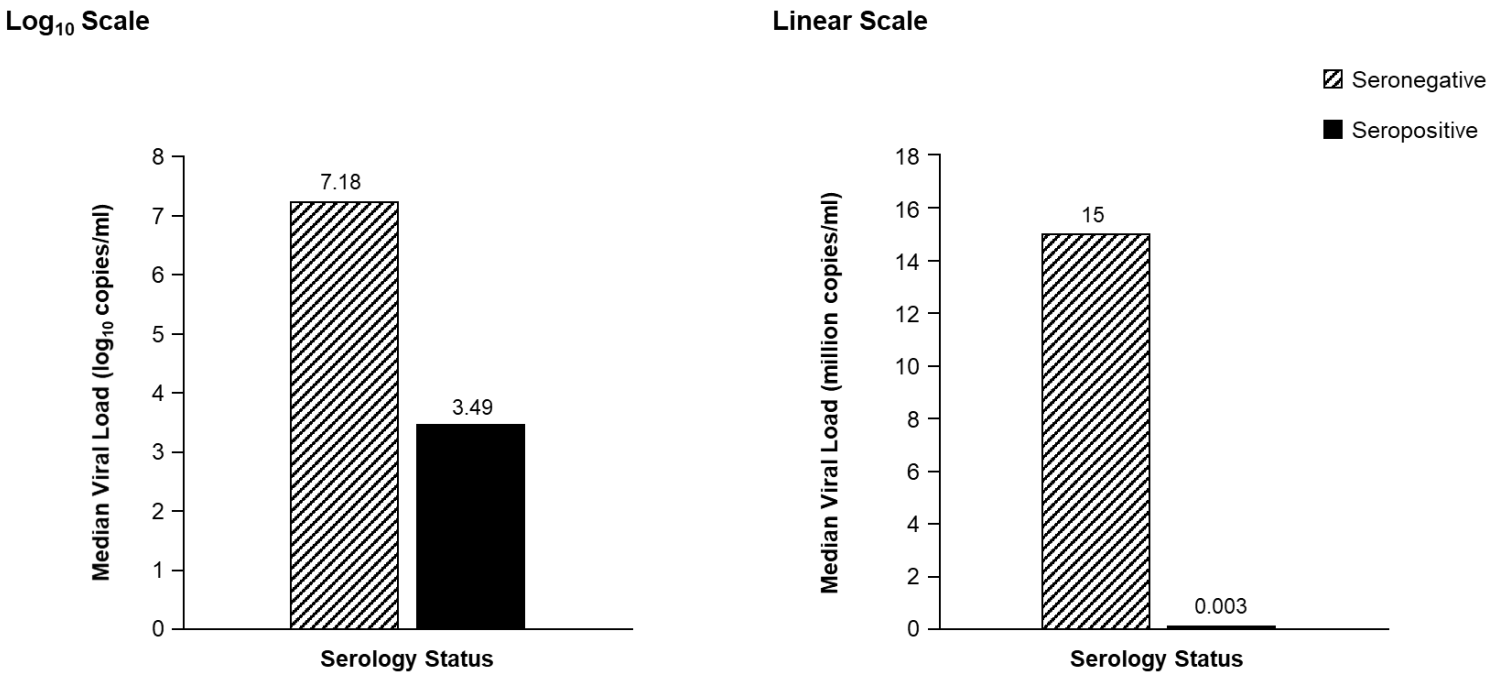
Supplementary Figures

Figure S1. Schematic Overview of the Study Design



*Serum samples for pharmacokinetic analysis were collected on day 3, 5, 7, and 15 in the phase 1 part only.
AESI, adverse event of special interest; con med, concomitant medication; eCOA, electronic clinical outcome assessment; IV, intravenous(ly); NP, nasopharyngeal; R, randomized; SAE, serious adverse event.

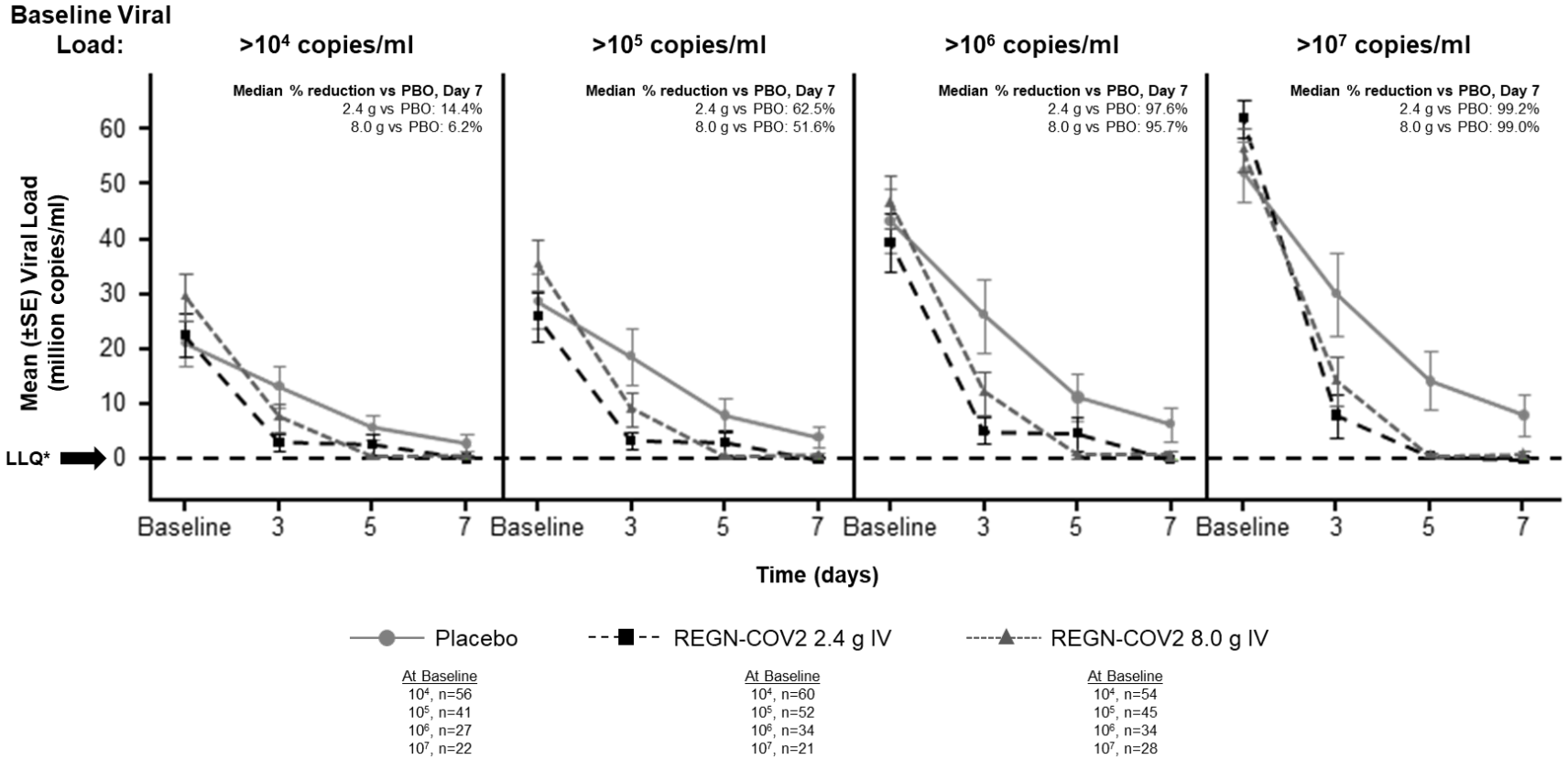
Figure S2. Relationship Between Baseline Serology Status and Baseline Viral Load



No. of Patients by Serology Status	Median (Q1, Q3) Viral Load in Nasopharyngeal Swabs, Log_{10} Scale:	Median (Q1, Q3) Viral Load in Nasopharyngeal Swabs, Linear Scale:	Median Time of Covid-19 Symptoms Before Randomization:
Seronegative: 113/275 (41.1%) Seropositive: 123/275 (44.7%) Other: 39/275 (14.2%)	Seronegative: 7.18 (5.88, 7.85) log_{10} copies/ml Seropositive: 3.49 (2.55, 4.52) log_{10} copies/ml	Seronegative: 15 (0.767, 71) million copies/ml Seropositive: 3,105 (357, 33,050) copies/ml	3.0 days

Q, quartile.

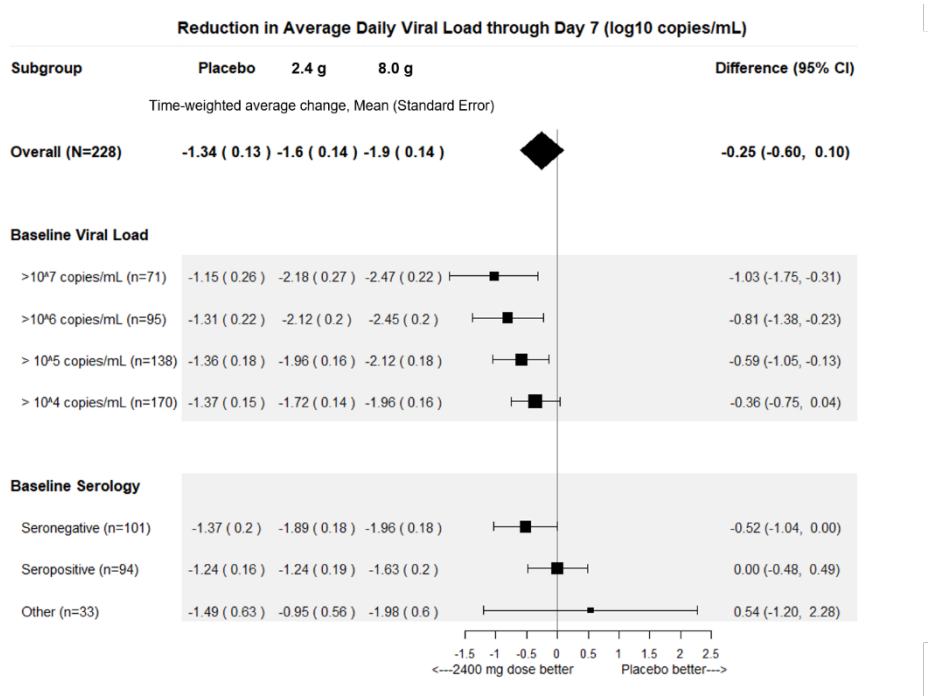
Figure S3. SARS-CoV-2 Viral Load (raw values) Over Time by Baseline Viral Load Category



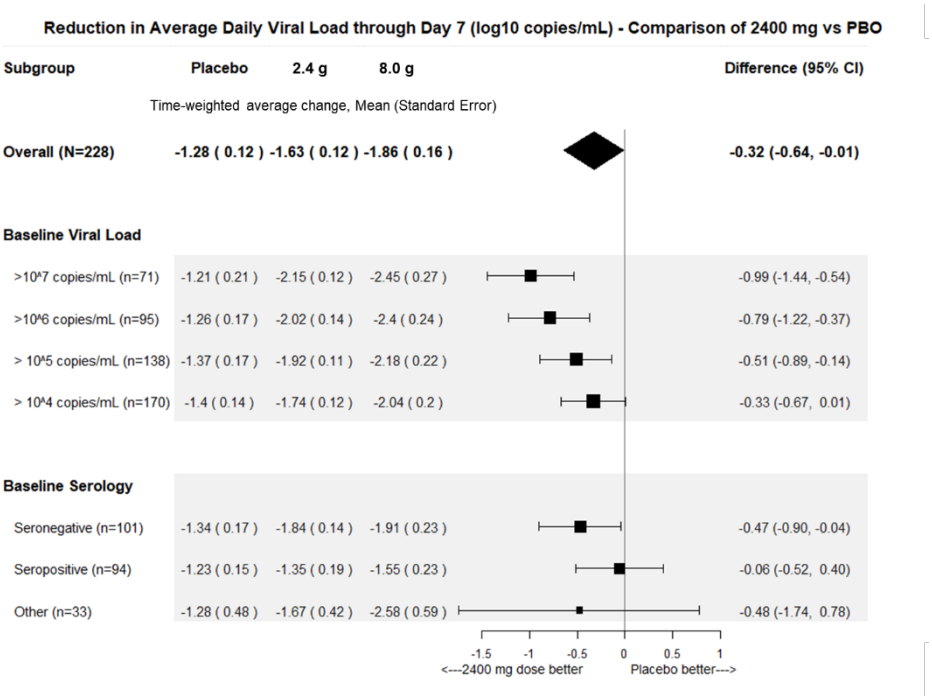
*The LLQ is 714 copies/ml.
IV, intravenous(ly); LLQ, lower limit of quantification; PBO, placebo; SE, standard error.

Figure S4. Time-weighted Average Change from Baseline (Day 1) through Day 7 with REGN-COV2 Treatment

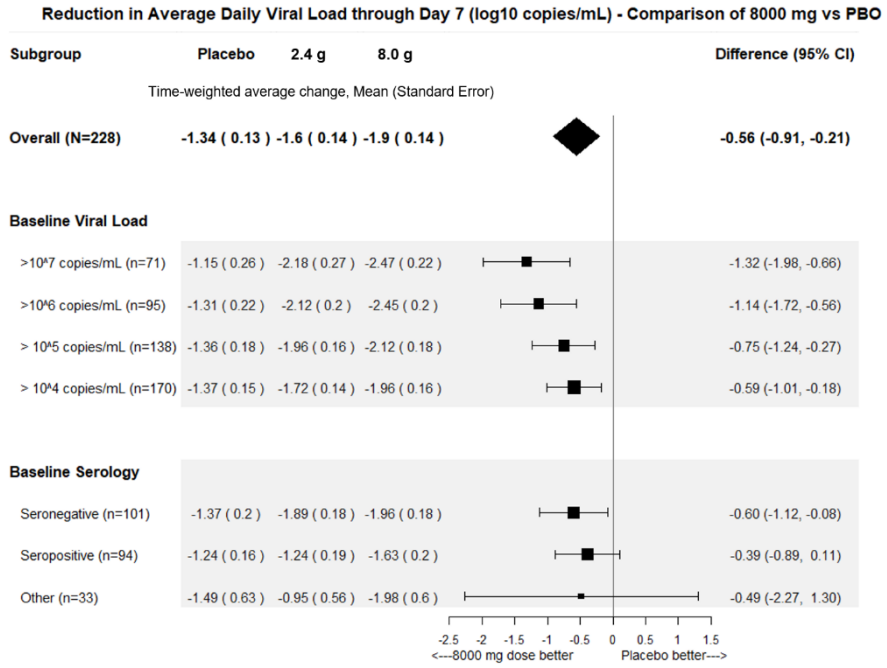
A. Mean Viral Load through Day 7 (log_{10} copies/ml) – Comparison of 2.4 g REGN-COV2 vs Placebo (Covariate-adjusted Means)*



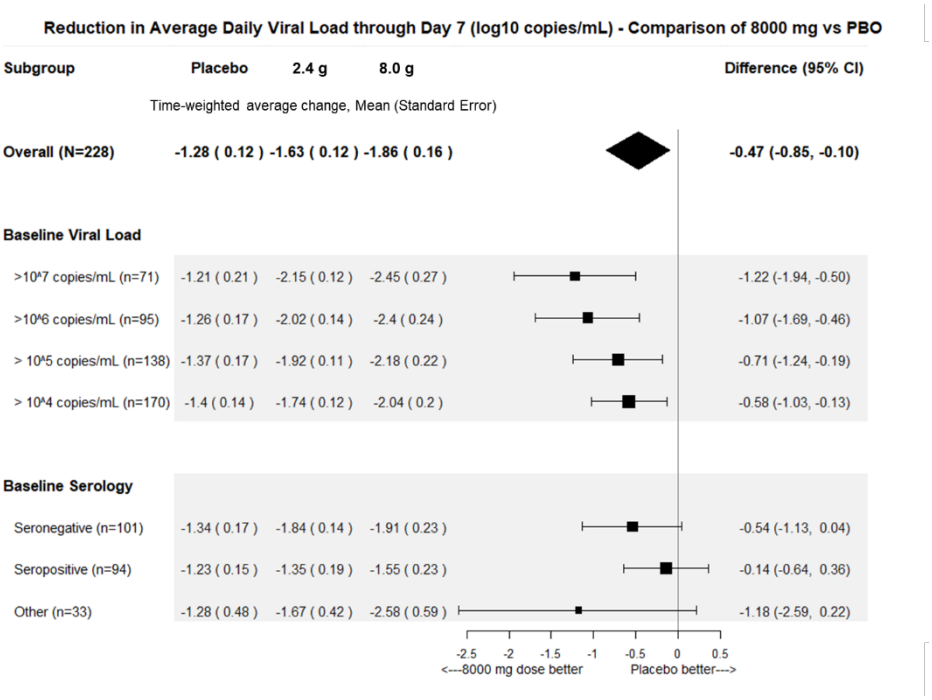
B. Mean Viral Load through Day 7 (log_{10} copies/ml) – Comparison of 2.4 g REGN-COV2 vs Placebo (Unadjusted Means)*



C. Mean Viral Load through Day 7 (log_{10} copies/ml) – Comparison of 8.0 g REGN-COV2 vs Placebo (Covariate-adjusted Means)*



D. Mean Viral Load through Day 7 (log_{10} copies/ml) – Comparison of 8.0 g REGN-COV2 vs Placebo (Unadjusted Means)*

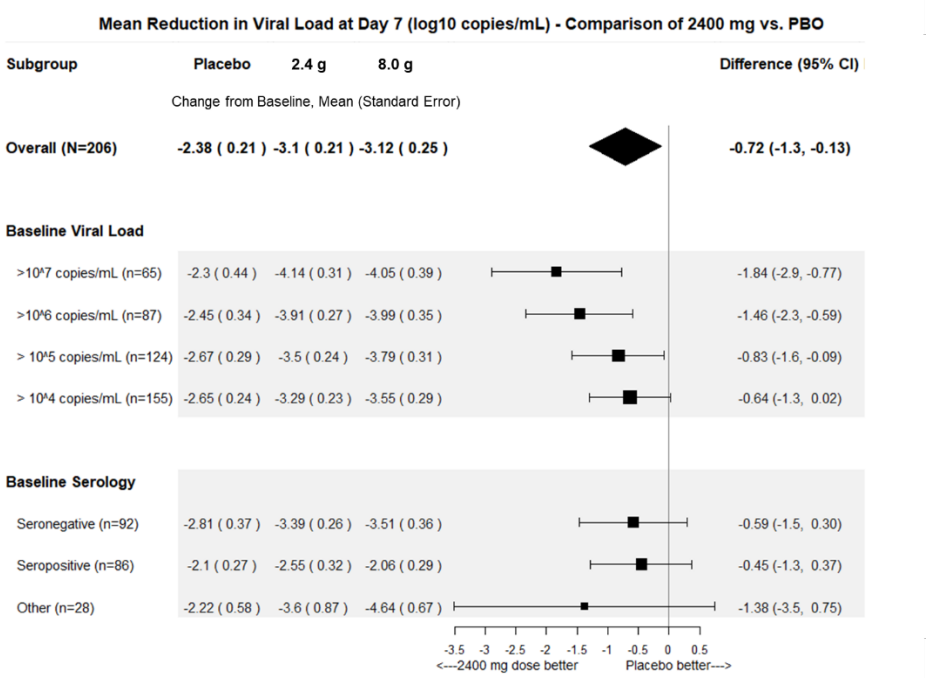


*Adjusted analysis of time-weighted average (TWA) change from baseline in viral load (log_{10} copies/ml) was based on Analysis of Covariance (ANCOVA) model with treatment group, risk factor, and baseline serology status as fixed effects, and baseline viral load and treatment by baseline viral load as covariates.

Unadjusted analysis of TWA change from baseline in viral load (log_{10} copies/ml) was based on two-sample t-test.

Figure S5. Mean Change from Baseline (Day 1) at Day 7 with REGN-COV2 Treatment

A. Mean Viral Load at Day 7 (log_{10} copies/ml) – Comparison of 2.4 g REGN-COV2 vs Placebo (Unadjusted Means)



B. Mean Viral Load at Day 7 (log_{10} copies/ml) – Comparison of 8.0 g REGN-COV2 vs Placebo (Unadjusted Means)

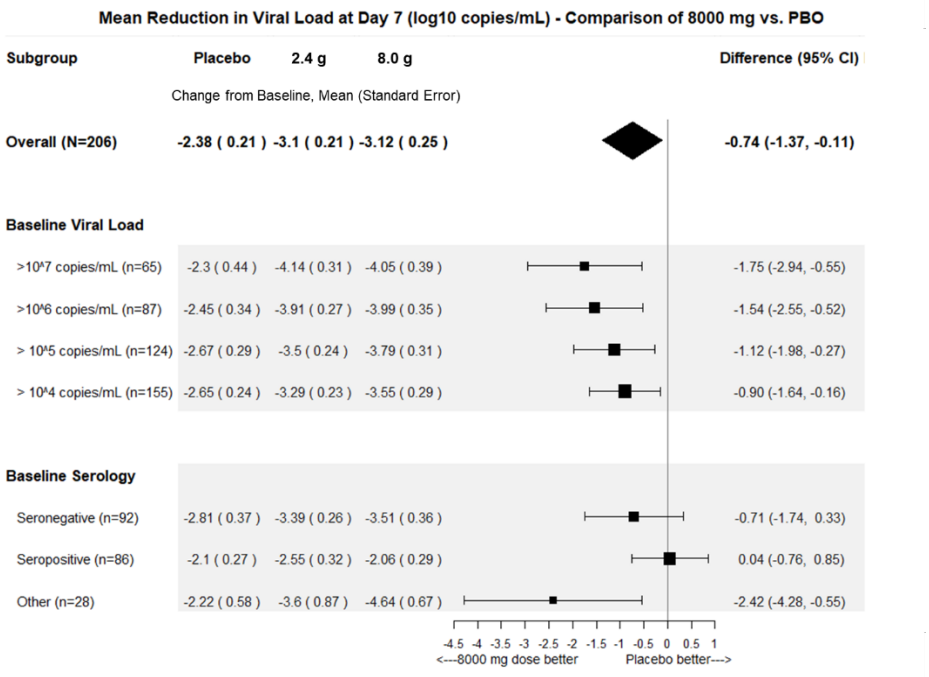
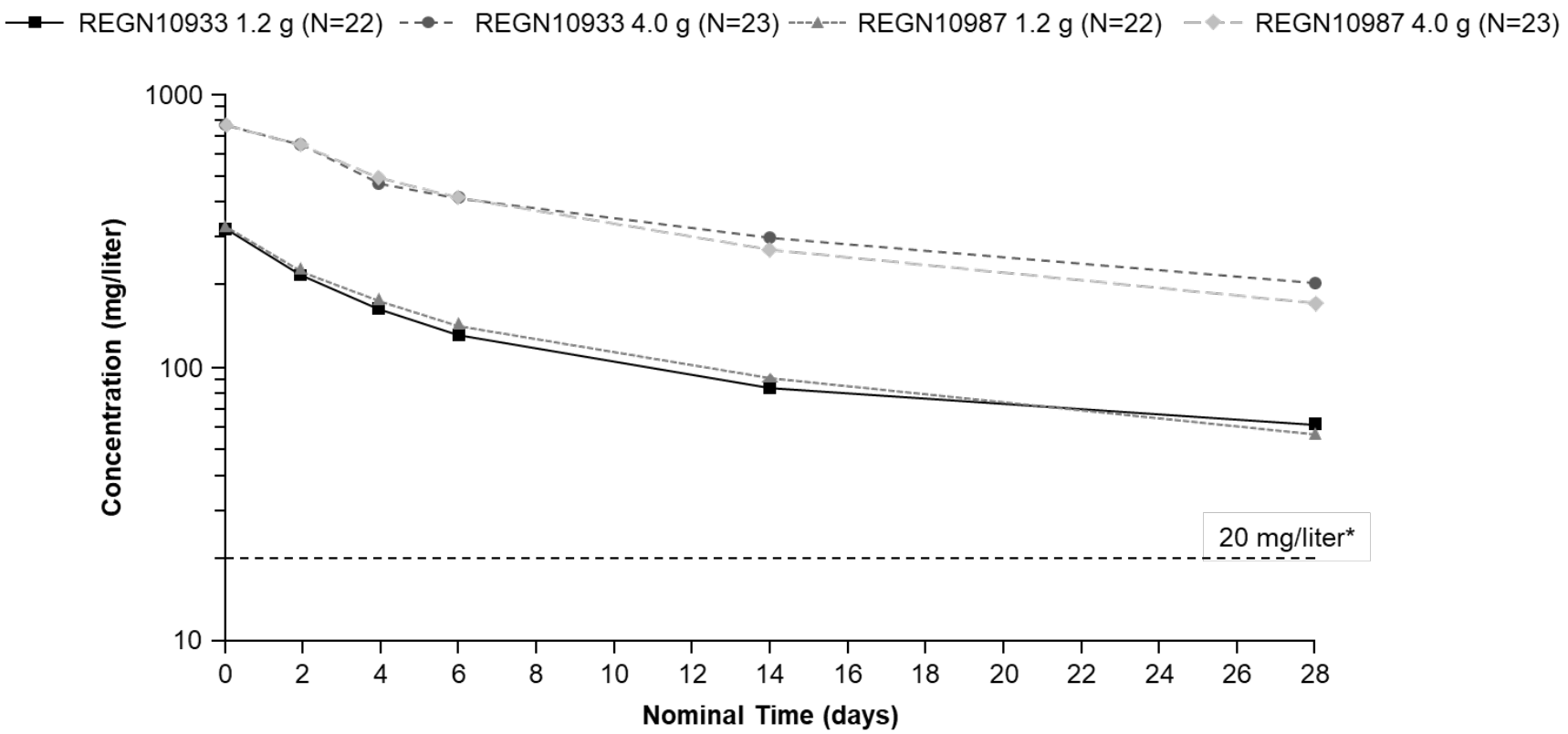


Figure S6. Median Concentrations of REGN10933 and REGN10987 in Serum Over Time



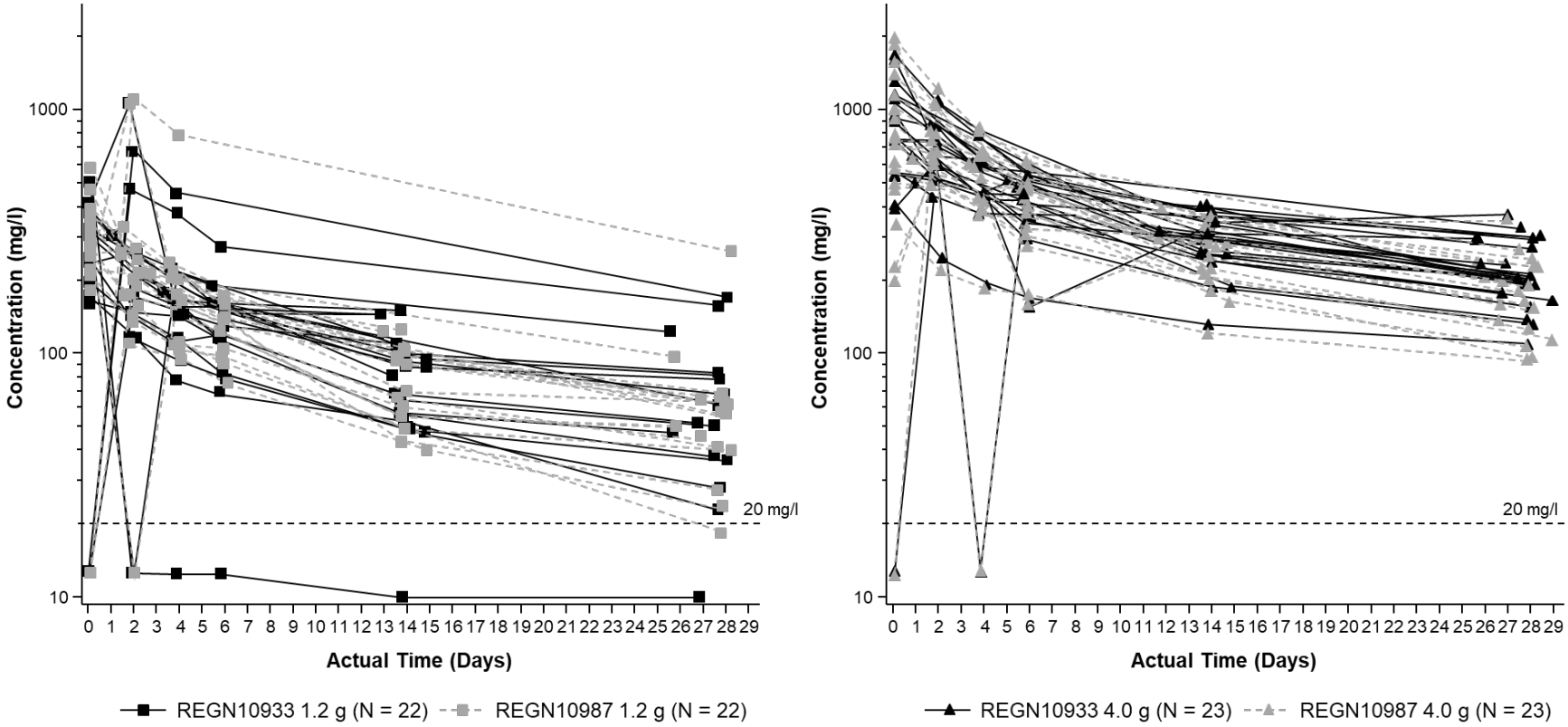
No.						
REGN10933 1.2 g	13	20	20	17	18	17
REGN10987 1.2 g	14	20	20	17	18	17
REGN10933 4.0 g	20	19	18	17	21	20
REGN10987 4.0 g	21	19	18	17	21	20

*Estimated therapeutic level

Figure S7. Individual Concentrations of REGN10933 and REGN10987 in Serum Over Time for Phase 1 Patients

A. 1.2 g per Monoclonal Antibody

B. 4.0 g per Monoclonal Antibody



Supplementary Tables

Table S1. Demographics and Baseline Characteristics by Serology Status

Baseline Serology Status: Negative					
	Total (N=113)	**Placebo Group (N=33)**	**REGN-COV2 2.4 g IV Group (N=41)**	**REGN-COV2 8.0 g IV Group (N=39)**	**REGN-COV2 Combined (N=80)**
Demographics					
Median age (Q1:Q3) — yr	43.0 (35.0:52.0)	43.0 (37.0:51.0)	41.0 (31.0:51.0)	45.0 (35.0:53.0)	43.0 (35.0:52.0)
Male sex — no. (%)	50 (44.2)	15 (45.5)	21 (51.2)	14 (35.9)	35 (43.8)
Hispanic or Latino ethnicity — no. (%)	46 (40.7)	9 (27.3)	22 (53.7)	15 (38.5)	37 (46.3)
Race — no. (%)					
White	92 (81.4)	26 (78.8)	33 (80.5)	33 (84.6)	66 (82.5)
Black or African American	12 (10.6)	5 (15.2)	5 (12.2)	2 (5.1)	7 (8.8)
Asian	2 (1.8)	1 (3.0)	0	1 (2.6)	1 (1.3)
Unknown	1 (0.9)	1 (3.0)	0	0	0
Not Reported	6 (5.3)	0	3 (7.3)	3 (7.7)	6 (7.5)

Median weight (Q1:Q3) — kg	86.00 (72.90:100.70)	83.00 (74.80:92.30)	86.30 (74.80:104.30)	86.20 (71.60:102.10)	86.25 (72.90:104.30)
Mean body-mass index (±SD)†	30.70±7.443	29.18±7.484	31.31±6.859	31.21±8.044	31.26±7.396
Obesity — no. (%)‡	52 (46.0)	13 (39.4)	19 (46.3)	20 (51.3)	39 (48.8)
Clinical Characteristics					
Baseline viral load in nasopharyngeal swab (raw values)					
Patients — no.	104	31	37	36	73
Mean (±SD) — copies/ml (10^6)	31.02±31.61	32.33±32.24	26.35±31.78	34.70±31.18	30.47±31.55
Median (Min:Max) — copies/ml	15000000 (1: 71000000)	14000000 (1:71000000)	2240000 (1:71000000)	32050000 (12200:71000000)	16000000 (1:71000000)
Baseline viral load in nasopharyngeal swab (log_{10} scale)					
Patients — no.	104	31	37	36	73
Mean (±SD) — log_{10} copies/ml	6.60±1.613	6.63±1.716	6.36±1.833	6.82±1.252	6.59±1.580
Median (range) — log_{10} copies/ml	7.18 (0.0–7.9)	7.15 (0.0–7.9)	6.35 (0.0–7.9)	7.51 (4.1–7.9)	7.20 (0.0–7.9)
Positive (≥LLOD) baseline qualitative RT-PCR — no. (%)	101 (89.4)	30 (90.9)	35 (85.4)	36 (92.3)	71 (88.8)

Baseline serum C-reactive protein					
Patients — no.	113	33	41	39	80
Median (Q1:Q3) — mg/liter	4.980 (1.890:12.200)	4.730 (1.670:11.770)	3.860 (1.540:8.920)	6.790 (2.620:20.620)	5.490 (2.015:13.275)
Median time from symptom onset to randomization (range) — days	3.0 (0–7)	3.0 (0–6)	3.5 (0–6)	3.0 (0–7)	3.0 (0–7)
Baseline Serology Status: Positive					
	Total (N=123)	**Placebo Group (N=47)**	**REGN-COV2 2.4 g IV Group (N=37)**	**REGN-COV2 8.0 g IV Group (N=39)**	**REGN-COV2 Combined (N=76)**
Demographics					
Median age (Q1:Q3) — yr	44.0 (35.0:53.0)	46.0 (34.0:58.0)	43.0 (34.0:51.0)	43.0 (37.0:53.0)	43.0 (36.0:51.5)
Male sex — no. (%)	65 (52.8)	28 (59.6)	20 (54.1)	17 (43.6)	37 (48.7)
Hispanic or Latino ethnicity — no. (%)	89 (72.4)	30 (63.8)	26 (70.3)	33 (84.6)	59 (77.6)
Race — no. (%)					
White	100 (81.3)	37 (78.7)	28 (75.7)	35 (89.7)	63 (82.9)
Black or African American	19 (15.4)	6 (12.8)	9 (24.3)	4 (10.3)	13 (17.1)
Asian	1 (0.8)	1 (2.1)	0	0	0

American Indian or Alaska Native	2 (1.6)	2 (4.3)	0	0	0
Not Reported	1 (0.8)	1 (2.1)	0	0	0
Median weight (Q1:Q3) — kg	84.60 (71.80:93.50)	84.80 (70.80:96.60)	84.25 (70.90:92.10)	85.15 (73.90:93.50)	84.45 (72.20:92.90)
Mean body-mass index (±SD)†	29.25±5.550	28.99±4.751	28.82±5.623	29.96±6.379	29.41±6.010
Obesity — no. (%)‡	44 (35.8)	16 (34.0)	12 (32.4)	16 (41.0)	28 (36.8)
Clinical Characteristics					
Baseline viral load in nasopharyngeal swab (raw values)					
Patients — no.	120	47	36	37	73
Mean (±SD) — copies/ml (10^6)	3.25±14.29	3.19±14.46	4.63±16.60	2.00±11.66	3.29±14.27
Median (Min:Max) — copies/ml	3105 (1:71000000)	4790 (1:71000000)	4460 (1:71000000)	1740 (1:71000000)	2240 (1:71000000)
Baseline viral load in nasopharyngeal swab (log_{10} scale)					
Patients — no.	120	47	36	37	73
Mean (±SD) — log_{10} copies/ml	3.30±2.146	3.42±2.088	3.42±2.409	3.05±1.979	3.23±2.194

Median (range) — log_{10} copies/ml	3.49 (0.0–7.9)	3.68 (0.0–7.9)	3.61 (0.0–7.9)	3.24 (0.0–7.9)	3.35 (0.0–7.9)
Positive (≥LLOD) baseline qualitative RT-PCR — no. (%)	94 (76.4)	38 (80.9)	27 (73.0)	29 (74.4)	56 (73.7)
Baseline serum C-reactive protein					
Patients — no.	123	47	37	39	76
Median (Q1:Q3) — mg/liter	2.860 (1.080:10.380)	4.030 (1.150:22.660)	2.080 (1.080:7.160)	2.770 (0.940:11.350)	2.245 (1.060:8.795)
Median (range) time from symptom onset to randomization — days	3.0 (0 to 8)	3.0 (0 to 8)	3.0 (0–6)	3.0 (0–8)	3.0 (0–8)
Baseline Serology Status: Unknown§					
	Total (N=39)	**Placebo Group (N=13)**	**REGN-COV2 2.4 g IV Group (N=14)**	**REGN-COV2 8.0 g IV Group (N=12)**	**REGN-COV2 Combined (N=26)**
Demographics					
Median age (Q1:Q3) — yr	44.0 (34.0:53.0)	44.0 (34.0:55.0)	45.5 (37.0:53.0)	44.5 (31.5:52.0)	44.5 (35.0:52.0)
Male sex — no. (%)	19 (48.7)	7 (53.8)	5 (35.7)	7 (58.3)	12 (46.2)

Hispanic or Latino ethnicity — no. (%)	18 (46.2)	7 (53.8)	4 (28.6)	7 (58.3)	11 (42.3)
Race — no. (%)					
White	32 (82.1)	9 (69.2)	13 (92.9)	10 (83.3)	23 (88.5)
Black or African American	4 (10.3)	3 (23.1)	1 (7.1)	0	1 (3.8)
Unknown	2 (5.1)	1 (7.7)	0	1 (8.3)	1 (3.8)
Not reported	1 (2.6)	0	0	1 (8.3)	1 (3.8)
Median weight (Q1:Q3) — kg	95.40 (76.70:105.20)	97.70 (76.70:124.00)	95.40 (72.00:105.20)	93.70 (80.60:102.30)	94.55 (72.00:105.20)
Mean body-mass index (±SD)†	32.43±9.184	34.19±12.161	31.85±7.698	31.10±7.540	31.55±7.461
Obesity — no. (%)‡	19 (48.7)	5 (38.5)	8 (57.1)	6 (50.0)	14 (53.8)
Clinical Characteristics					
Baseline viral load in nasopharyngeal swab (raw values)					
Patients — no.	34	13	11	10	21
Mean — copies/ml (10^6)	14.82±27.10	2.04±7.08	19.04±30.75	26.78±34.03	22.73±31.78
Median (Min:Max) — copies/ml	145500 (1:71000000)	82800 (357:25600000)	937000 (2200:71000000)	2320000 (1:71000000)	1490000 (1:71000000)

Baseline viral load in nasopharyngeal swab (log_{10} scale)					
Patients — no.	34	13	11	10	21
Mean (±SD) — log_{10} copies/ml	5.30±1.927	4.52±1.333	5.90±1.593	5.66±2.640	5.79±2.102
Median (range) — log_{10} copies/ml	5.15 (0.0–7.9)	4.92 (2.6–7.4)	5.97 (3.3–7.9)	6.34 (0.0–7.9)	6.17 (0.0–7.9)
Positive (≥LLOD) baseline qualitative RT-PCR — no. (%)	33 (84.6)	13 (100)	11 (78.6)	9 (75.0)	20 (76.9)
Baseline serum C-reactive protein					
Patients — no.	29	12	9	8	17
Median (Q1:Q3) — mg/liter	5.180 (1.900:16.830)	9.085 (2.150:31.410)	2.930 (1.750:5.700)	4.650 (2.215:11.600)	4.120 (1.790:6.370)
Median time from symptom onset to randomization (range) — days	4.0 (1–7)	2.0 (1–7)	4.0 (1–7)	5.0 (1–5)	4.0 (1–7)

†The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡Obesity is defined as body-mass index >30 kg/m^2.
§Patient serology status could not be evaluated or had borderline results.
IV, intravenous(ly); LLOD, lower limit of detection; Q, quartile; RT-PCR, reverse transcription polymerase chain reaction; SD, standard deviation.

Table S2. Relationship Between Baseline Viral Load Category and Reduction in Viral Load with REGN-COV2 Treatment

	Placebo Group	REGN-COV2 2.4 g IV Group	REGN-COV2 8.0 g IV Group	REGN-COV2 Combined
Viral load values (log_{10} scale) by baseline viral load at each visit through day 7, log_{10} copies/ml, mean (SD)				
>10^4 copies/ml				
mFAS	**n=56**	**n=60**	**n=54**	**n=114**
Baseline	6.16 (1.36)	6.36 (1.22)	6.53 (1.35)	6.44 (1.28)
Day 3	5.04 (2.04)	4.99 (1.37)	4.94 (2.00)	4.96 (1.70)
Day 5	4.25 (2.16)	4.13 (1.48)	3.83 (1.87)	3.99 (1.67)
Day 7	3.46 (2.32)	3.09 (1.63)	3.00 (2.05)	3.05 (1.83)
>10^5 copies/ml				
mFAS	**n=41**	**n=52**	**n=45**	**n=97**
Baseline	6.77 (1.05)	6.65 (1.04)	6.95 (1.04)	6.79 (1.04)
Day 3	5.86 (1.65)	5.10 (1.39)	5.35 (1.80)	5.22 (1.59)
Day 5	4.80 (2.14)	4.19 (1.57)	4.04 (1.86)	4.12 (1.70)
Day 7	4.06 (2.24)	3.19 (1.63)	3.23 (2.04)	3.21 (1.81)
>10^6 copies/ml				
mFAS	**n=27**	**n=34**	**n=34**	**n=68**
Baseline	7.44 (0.50)	7.26 (0.68)	7.45 (0.59)	7.36 (0.64)
Day 3	6.64 (1.13)	5.71 (1.02)	5.61 (1.88)	5.66 (1.50)
Day 5	5.73 (1.41)	4.67 (1.47)	4.36 (1.80)	4.52 (1.64)
Day 7	4.97 (1.95)	3.34 (1.60)	3.52 (2.04)	3.43 (1.82)
>10^7 copies/ml				
mFAS	**n=22**	**n=21**	**n=28**	**n=49**

Baseline	7.64 (0.31)	7.77 (0.16)	7.71 (0.22)	7.73 (0.20)
Day 3	6.79 (1.13)	6.15 (0.92)	5.82 (1.94)	5.96 (1.58)
Day 5	6.04 (1.35)	4.96 (0.80)	4.41 (1.90)	4.65 (1.54)
Day 7	5.36 (2.05)	3.63 (1.46)	3.66 (2.07)	3.65 (1.81)
Viral load values (raw values) by baseline viral load at each visit through day 7, million copies/ml, mean (SD)				
>10^4 copies/ml				
mFAS	**n=56**	**n=60**	**n=54**	**n=114**
Baseline	21.05 (30.01)	22.52 (30.67)	29.46 (31.67)	25.81 (31.20)
Day 3	13.19 (25.96)	3.07 (10.57)	7.50 (18.09)	5.22 (14.81)
Day 5	5.82 (15.73)	2.63 (12.90)	0.29 (0.75)	1.53 (9.42)
Day 7	2.91 (10.21)	0.02 (0.06)	0.46 (2.63)	0.23 (1.80)
>10^5 copies/ml				
mFAS	**n=41**	**n=52**	**n=45**	**n=97**
Baseline	28.73 (31.81)	25.97 (31.57)	35.35 (31.55)	30.32 (31.74)
Day 3	18.62 (29.25)	3.43 (11.38)	9.10 (19.60)	6.14 (16.01)
Day 5	7.96 (17.98)	3.01 (13.78)	0.36 (0.81)	1.80 (10.23)
Day 7	4.04 (11.88)	0.03 (0.06)	0.56 (2.91)	0.27 (1.96)
>10^6 copies/ml				
mFAS	**n=27**	**n=34**	**n=34**	**n=68**
Baseline	43.45 (29.98)	39.50 (31.55)	46.69 (28.02)	43.09 (29.83)
Day 3	26.13 (32.17)	5.08 (13.63)	11.96 (22.13)	8.52 (18.55)
Day 5	11.30 (21.42)	4.65 (17.02)	0.46 (0.92)	2.59 (12.23)
Day 7	6.31 (14.48)	0.03 (0.05)	0.73 (3.29)	0.37 (2.30)
>10^7 copies/ml				
mFAS	**n=22**	**n=21**	**n=28**	**n=49**

Baseline	52.34 (25.78)	62.00 (15.83)	56.27 (20.50)	58.72 (18.68)
Day 3	30.08 (32.96)	8.04 (16.90)	14.23 (23.55)	11.62 (21.01)
Day 5	14.21 (23.30)	0.39 (0.81)	0.52 (0.99)	0.46 (0.91)
Day 7	8.06 (16.01)	0.03 (0.06)	0.83 (3.53)	0.49 (2.68)

IV, intravenous(ly); mFAS, modified full analysis set; SD, standard deviation.

Table S3. Treatment-Emergent Serious Adverse Events and Adverse Events of Special Interest Reported in Subjects Receiving REGN-COV2

System Organ Class Preferred Term	**Placebo Group (N=93)**	**REGN-COV2 2.4 g IV Group (N=88)**	**REGN-COV2 8.0 g IV Group (N=88)**	**REGN-COV2 Combined (N=176)**
Serious Adverse Events*				
Gastrointestinal disorders				
Vomiting	0	1 (1.1%)	0	1 (0.6%)
Nausea	0	1 (1.1%)	0	1 (0.6%)
Vascular disorders				
Hypertension	1 (1.1%)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Hypoxia	1 (1.1%)	0	0	0
Adverse Events of Special Interest*				
Gastrointestinal disorders				
Abdominal pain	0	0	1 (1.1%)	1 (0.6%)
Vomiting	1 (1.1%)	0	0	0
Nausea	1 (1.1%)	0	0	0
Skin and subcutaneous tissue disorders				
Pruritus	0	0	1 (1.1%)	1 (0.6%)
Urticaria	0	0	1 (1.1%)	1 (0.6%)
Rash	1 (1.1%)	0	0	0
General disorders and administration site conditions				
Chills	0	0	1 (1.1%)	1 (0.6%)
Vascular disorders				
Flushing	0	0	1 (1.1%)	1 (0.6%)
Nervous system disorders				
Dizziness	1 (1.1%)	0	0	0
Headache	1 (1.1%)	0	0	0

*Only serious adverse events and adverse events of special interest (≥ grade 2 infusion-related reactions and hypersensitivity reactions) were collected.
IV, intravenous(ly).

Table S4. Mean Pharmacokinetic Parameters

Pharmacokinetic Parameter, mean (SD) [N]*	REGN10933		REGN10987	
	1.2 g	4.0 g	1.2 g	4.0 g
C_{max} (mg/l)	325 (214) [22]	875 (349) [23]	364 (265) [22]	923 (424) [23]
AUC_{0-28} (mg•day/l)	3393 (1887) [16]	9775 (2464) [19]	3492 (2916) [17]	9218 (2629) [19]
C_{28} (mg/l)†	68.0 (45.2) [17]	219 (69.0) [20]	64.9 (53.9) [17]	181 (64.9) [20]
$t_{1/2}$ (days)	37.4 (19.5) [12]	29.1 (9.33)‡§ [17]	34.4 (25.5) [13]	25.1 (18.1)‡ [18]

*Number of observations
†Observed concentration 28 days after dosing, i.e. on day 29
‡One patient excluded as day 29 concentration was greater than day 14, the resulting positive slope precluded estimation of $t_{1/2}$
§One patient with an estimated $t_{1/2}$ of 536 days was identified as an outlier and therefore not reported
AUC, area under the curve; C, concentration; $C_{max,}$ maximum concentration; SD, standard deviation; $t_{1/2,}$ half-life.

Table S5. Summary Statistics of Half-life for REGN10933 and REGN10987

	Dose	N*	Mean	SD	Min	Median	Max	CV%
10933	1.2 g	12	37.4	19.5	11.4	32.2	73.5	52.1
10987	1.2 g	13	34.4	25.5	9.9	26.2	90.9	74.2
10933†	4.0 g	17‡	29.1	9.33	13.3	27.7	50.5	32.1
10987	4.0 g	18‡	25.1	18.08	13.18	20.79	94.48	72.03

*Summary statistics determined from patients with a determinable $t_{1/2}$ (excluding one patient as an outlier).
†One patient with a determined $t_{1/2}$ of 536 days was identified as an outlier and excluded from these summary statistics.
‡One patient excluded as the concentrations at day 29 were greater than day 14 resulting in a positive slope precluding $t_{1/2}$ determination
SD, standard deviation.

Appendix References

1. Vandergaast R, Carey T, Reiter S, et al. Development and validation of IMMUNO-COV™: a high-throughput clinical assay for detecting antibodies that neutralize SARS-CoV-2. bioRxiv 2020:2020.05.26.117549.