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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A MASTER PROTOCOL ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF HOSPITALIZED PATIENTS WITH COVID-19

Compound:	REGN10933+REGN10987
Clinical Phase:	1/2/3
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Medical/Study Director:	[redacted]

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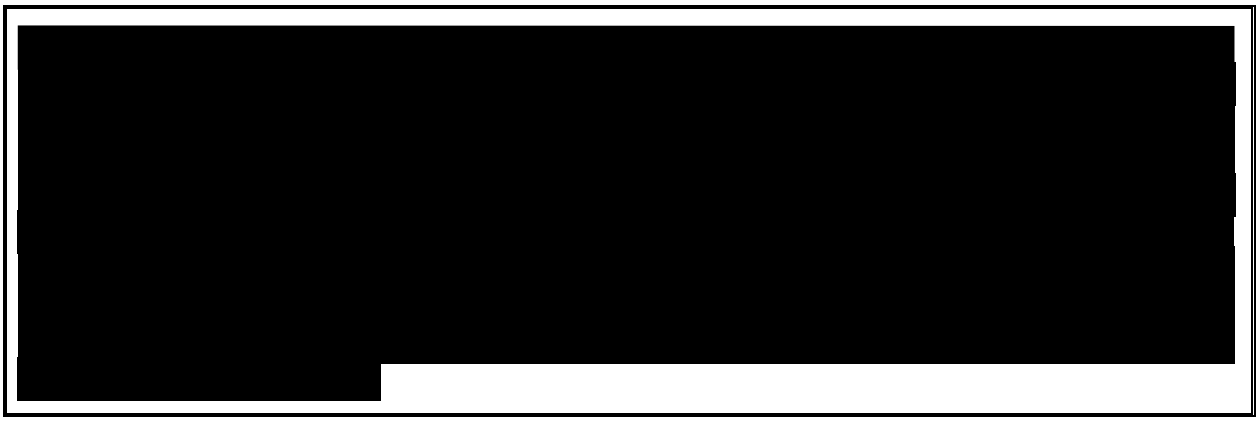

AMENDMENT HISTORY

Amendment 9 US

The primary purpose of this US-specific amendment is to amend the long COVID sub-study to allow the collection of additional diagnostic information to contextualize any symptoms or diagnoses that may confound or be associated with long COVID.

Description of Change	Brief Rationale	Section(s)
For patients in the long COVID sub-study, any new medical condition(s) diagnosed after randomization will be captured as an adverse event of special interest (AESI), but will not require expedited reporting to the Sponsor. Patients who previously consented to the long COVID sub-study but have already completed their end of study visit may be reconsented for retrospective collection of this information.	To contextualize any symptoms or diagnoses that may confound or be associated with long COVID	Table 3 Schedule of Events for the Long COVID Sub-Study at Participating Sites Section 9.1.2.1 Footnotes for Table 2 and Table 3 Schedule of Events (Phase 2 and Phase 3), #19 [new] Section 9.2.9.4 Recording New Medical Diagnoses or Conditions [new] Section 10.1.1 General Guidelines Section 10.1.4 Other Adverse Events of Special Interest that do not Require Expedited Reporting to Sponsor [new]
In the long COVID sub-study, any positive SARS-CoV-2 local test results obtained outside of the study (starting from the day at which they consent to protocol amendment 9 US) will no longer require expedited reporting to the Sponsor.	To provide operational flexibility	Section 4.3 Exploratory Endpoints Section 9.2.9.3 Monitoring for SARS-CoV-2 Reinfection Section 10.1.3 Events that Require Expedited Reporting to Sponsor Section 10.1.4 Other Adverse Events of Special Interest that do not Require Expedited Reporting to Sponsor [new]
Risk-benefit information was updated with topline phase 3 data showing clinical benefit of REGN10933+REGN10987.	To provide current study drug information	Section 3.3 Risk-Benefit Section 3.3.1 Summary of Efficacy and Safety Profile in Clinical Trials Section 3.3.2 Summary of Risks
It was clarified that coagulation tests will not be collected as part of the long COVID sub-study.	To provide clarity for sample collection	Section 9.1.2.1 Footnotes for Table 2 and Table 3 Schedule of Events (Phase 2 and Phase 3), #12
Minor updates (typographical, editorial, administrative) were made.	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 8 US

The primary purpose of this US-specific amendment is to implement a sub-study to obtain a better understanding of long COVID and the potential impact of treatment during acute infection on the longer-term phase of COVID-19.

Description of Change	Brief Rationale	Section(s)
Evaluation of Long COVID		
A long COVID sub-study will be conducted at select sites through day 180 in phase 2 (cohort 1A) and phase 3 (cohort 1). The sub-	To better understand the patient experience of long COVID, and to evaluate	Clinical Protocol Synopsis: Study Design

Description of Change	Brief Rationale	Section(s)
study will evaluate patient-reported symptoms and related outcomes. In addition, blood samples will be collected for biomarker analysis and immunoprofiling, to gain a better understanding of the underlying biology of long COVID and the impact of prior treatment in the acute stage of disease. Nasopharyngeal (NP) swab samples will also be collected to assess for the presence of SARS-CoV-2 during this later stage of analysis.	whether treatment of initial SARS-CoV-2 infection with study drug may provide subsequent clinical benefit in the prevention of long COVID	Section 1.3 Long-Term Outcomes in Patients with COVID-19 Section 2.3 Exploratory Objectives Section 3.2.1.7 Long COVID Sub-Study Section 4.3 Exploratory Endpoints Section 5.6 Pharmacodynamic and Other Biomarker Variables Section 6.1.2 Study Duration Figure 3 Study Flow Diagram, Phase 2 and Phase 3 Section 7.2.1 Inclusion Criteria, #6 Section 9.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) and Phase 3 (Cohort 1) Table 3 Schedule of Events for the Long COVID Sub-Study at Participating Sites [new] Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2 and Phase 3), #3; #16, 17 [new] Section 9.2.9 Long COVID Sub-Study (at Participating Sites) Table 4 Symptoms Evaluated in the Symptom Evolution of Long COVID-19 (SE-LC19) Instrument Section 11.4.8 Exploratory Analysis [new]
For patients in the long COVID sub-study any positive SARS-CoV-2 local test result, obtained from the day of consent to the long COVID sub-study until day 180, will be recorded and reported as an AESI	To provide additional contextual information regarding SARS-CoV-2 infection to inform long COVID analyses	Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2 and Phase 3), #18 [new] Section 9.2.9.3 Monitoring for SARS-CoV-2 Reinfection Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Clarified that, for the optional pharmacogenomics sub-study, patients who consent to this sub-study will only have a blood sample collected for DNA. Patients who already consented to the sub-study will not be consented a second time, and patients who have already provided a sample for the PGx sub-study should not have a second sample collected.	To ensure appropriate collection of sub-study samples.	Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2 and Phase 3), #3 Section 9.2.9.4 Pharmacogenomic Analysis (Optional)
Clarified that although patient-reported outcome (PRO) data (eg, patient-reported questionnaires, surveys, and instruments) are generally not reportable as individual AEs, if the investigator is made aware of any AE that (in his or her judgement) is related to study drug, the AE will follow standard AE reporting and recording.	To ensure appropriate collection of safety-related data.	Section 9.2.9 Long COVID Sub-Study (at Participating Sites) Section 10.1.1 General Guidelines

Description of Change	Brief Rationale	Section(s)
Updates to background information, minor clarifications for consistency, administrative changes, and other minor updates (typographical, editorial, formatting) were made.	To ensure clarity, accuracy, and consistency.	Throughout the document

Amendment 7

The primary purpose of this amendment is to update the planned statistical analysis for the final analysis, including changes to the objectives and endpoints, following early termination of the study on 09 April 2021 based on a Sponsor business decision.

The following table outlines all changes made to the protocol and the affected sections.

Description of Change	Brief Rationale	Section(s)
Key modifications to the planned final statistical analysis include the following. **Efficacy analysis** The primary virological and clinical analyses will involve pooling of cohort 1 (hospitalized on low-flow oxygen) and cohort 1A (hospitalized but not requiring supplemental oxygen) and doses. Assessment of each cohort and dose alone will now be secondary. The primary **virologic endpoint** is time-weighted average change from baseline viral load in nasopharyngeal (NP) sample through day 7 in the Seronegative mFAS in the **pooled** phase 3 cohort 1 and phase 2 cohort 1A, and combined across the 2.4 g and 8.0 g doses of REGN10933+REGN10987. The primary **clinical endpoint** is the proportion of patients who died or went on mechanical ventilation from day 6 through day 29 and from day 1 through day 29. The primary analysis will be performed for the High Viral Load mFAS, Seronegative mFAS, and Overall mFAS in the **pooled** phase 3 (cohort 1) and phase 2 (cohort 1A). To control alpha at a strict 0.05 level, the two primary endpoints will be tested hierarchically, with the virologic endpoint tested first. All hierarchical testing will be done using the **combined** dose group. There are no primary objectives for phase 2 cohort 1A, as enrollment was prematurely terminated. The clinical efficacy endpoints for phase 3 (cohort 1) and phase 2 (cohort 1A), separately, will be assessed as secondary.	**For efficacy analysis** As a result of the study ending early and the resultant constrained sample size, cohorts and doses will be pooled in the primary virological and clinical analyses to enhance the ability to detect clinically meaningful treatment effects. To assess the potential efficacy of REGN10933+REGN10987 using relevant measures in a patient population most likely to receive benefit from the therapy, based on preliminary data from clinical studies of REGN10933+REGN10987 in hospitalized patients (Regeneron, 2020) (Horby, 2021). The clinical efficacy of phase 3 (cohort 1) and phase 2 (cohort 1A), separately, will be assessed as secondary due to constrained sample size following early study termination.	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.3 Planned Interim Analysis Section 7.1 Number of Patients Enrolled Section 11 Statistical Plan (and sections therein)

Description of Change	Brief Rationale	Section(s)
Safety analysis The safety analysis will be performed for the following cohorts, separately. Patients in phase 1/2 (cohort 1) and phase 2 (cohort 2 and cohort 3) are included in these analyses since more safety data were collected for the patients after the previous database lock on 22 December 2020: • Phase 2 (cohort 1A) • Phase 2 (cohort 2) • Phase 2 (cohort 3) • Phase 1/2/3 (cohort 1) combined **Pharmacokinetics (PK) and immunogenicity analysis** The PK and anti-drug antibody (ADA) analysis will be performed for phase 1/2/3 (cohort 1) combined, phase 2 (cohort 1A), phase 2 (cohort 2), and phase 2 (cohort 3), separately. The neutralizing antibody (NAb) analysis will only be performed for phase 2 and phase 3 patients.	**For safety and PK analysis** To specify the safety and PK analysis populations based on patient enrollment	
It was noted that the Sponsor made a business decision to terminate patient enrollment in this study on 09 April 2021, and this decision was not based on any safety concerns. Patients who have been enrolled will be continued to be followed up according to the Schedule of Events. In addition, enrolled patients at select sites may be reconsented and followed for an extended period for the long COVID sub-study.	Study terminated due to extremely low recruitment rates over several months	Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Hospitalized Patients with COVID-19 Section 6.1 Study Description and Duration Section 7.1 Number of Patients Enrolled
Minor clarifications and edits were made, including: • Treatments related to reported adverse events (AEs), such as supplemental oxygen and packed red blood cells, were added to the list of targeted concomitant medications and procedures • Collection details for oxygen delivery device status were updated to clarify timing • For individual patients, study completion is defined as the completion of the Schedule-of-Events-defined end of study visit, including vital status information collection. • Clarified that post-discharge study visits may occur by phone **or** in person • In addition to anti-drug antibodies (ADA), neutralizing antibodies (NAb) against REGN10933+REGN10987 will be assessed in phase 2 and phase 3.	To provide clarity	Section 3.2.1.4 Patient Population and Study Cohorts Section 3.3 Risk-Benefit Section 5.5 Immunogenicity Variables Section 6.1.6 Definition of Study Completion Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2 and Phase 3), footnotes #10 Section 9.2.3.3 Targeted Medication and Procedure Review Section 9.2.5.2 Clinical and Oxygen Status Section 10.1.2 Reporting Procedure

Description of Change	Brief Rationale	Section(s)
• The risk-benefit section and background information were updated.		
Risk-benefit information was updated to reflect the current Investigator's Brochure.	To provide current safety information	Section 3.3 Risk-Benefit
Updated reiteration of IDMC recommendation for an enrollment hold of cohort 2 and cohort 3 as of 19 February 2021.	To ensure current information	Throughout the document
Minor editorial changes have been made to accurately reflect the current statistical analysis and cohort designations.	To ensure accuracy and readability	Throughout the document
Updates to background information, minor clarifications for consistency, and other minor updates (typographical, editorial, formatting) were made.	To ensure clarity, accuracy, and consistency.	Throughout the document

Amendment 6

The primary purpose of this amendment is to update the planned statistical analysis for the phase 1/2 portion of the study prior to unblinding. The primary analysis of phase 1/2 (cohort 1) will exclude futility of REGN10933+REGN10987 compared with placebo, as measured by death or mechanical ventilation. If the study as designed is determined not to be futile, the clinical efficacy of REGN10933+10987 in reducing death or mechanical ventilation will be evaluated as a key secondary endpoint.

Other updates include incorporating the current IDMC recommendation to hold cohort 2/3 enrollment, pending further review of data.

Description of Change	Brief Rationale	Section(s)
Key modifications to the planned statistical analysis include the following: • The primary objective of phase 1/2 cohort 1 will be to exclude futility of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation. If futility is declared, the phase 1/2 data will be analyzed descriptively • If the study as designed is determined not to be futile, the clinical efficacy of REGN10933+10987 in reducing death or mechanical ventilation will be evaluated as a key secondary endpoint in cohort 1. This endpoint will be tested using a statistical hierarchy • The statistical hierarchy of key secondary endpoints will focus on assessments in: 1) patients who are seronegative at baseline and do not have a negative baseline RT-qPCR; 2) patients who do not have a negative baseline RT-qPCR and have high viral load	To determine future direction of program and assess the potential efficacy of REGN10933 + REGN10987 using clinically-relevant measures in a patient population most likely to receive benefit from an anti-viral therapy	Clinical Study Protocol Synopsis: Objectives, Study Design, Endpoints, Statistical Plan Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.1 Hypotheses Section 3.2.1.5 Rationale for Primary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 4.2.1 Key Secondary Endpoint [new] Section 4.2.2 Other Secondary Endpoints [new] Section 6.1 Study Description and Duration Section 6.3 Planned Interim Analysis Section 11 Statistical Plan Section 11.1.1 Statistical Hypotheses Section 11.2 Justification of Sample Size Section 11.3.1 Efficacy Analysis Sets

Description of Change	Brief Rationale	Section(s)
• Virologic efficacy will be analyzed descriptively as secondary endpoints for all cohorts • Additional relevant changes have been made as needed to the statistical analysis section, including power calculations and methods of analyses (eg, Kaplan-Meier and hazard ratio) Additional details are provided in the phase 1/2 Statistical Analysis Plan (SAP).		Section 11.4.3.1 Primary Futility and Key Secondary Efficacy Analysis Section 11.4.3.2 Other Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Section 11.4.5.1 Adverse Events Section 11.5 Interim Analysis
Per IDMC recommendation initially received on 30 October and reiterated on 18 November and 10 December 2020, patient enrollment in cohort 2 and cohort 3 has been placed on hold pending IDMC review of further data. Patient enrollment in cohort 1A and cohort 1 will continue. All currently enrolled patients will continue to follow the protocol schedule to which they were last consented.	Per IDMC recommendation based on a potential safety signal and an unfavorable risk-benefit profile in cohorts 2 and 3 at this time	Clinical Study Protocol Synopsis: Population Section 3.2.1.4 Patient Population and Study Cohorts Section 6.1 Study Description and Duration Section 6.1.1 Study Design Section 6.1.2 Study Duration Figure 3 Study Flow Diagram, Phase 2 Section 6.1.3 Description of Study Cohorts Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #5 Section 8.6 Method of Treatment Assignment Section 9.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.2.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.4.3.2 Other Secondary Efficacy Analysis
Any cohort 1 patient enrolled after the first 691 cohort 1 patients (including the 60 patients from phase 1) will be considered part of phase 3. These patients will follow the phase 2 Schedule of Events. The number of enrolled and planned patient was also updated.	To ensure accurate description of study phase enrollment	Clinical Study Protocol Synopsis: Population Section 6.1.1 Study Design Section 9.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*)
The number of patients enrolled to date and planned to be enrolled was updated	To ensure accurate description of study phase enrollment	Section 7.1 Number of Patients Planned
Patients who have received anti-SARS-CoV-2 mAbs (eg, bamlanivimab) within 5 months prior to randomization will be excluded.	To avoid potential confounding factors for clinical efficacy and safety assessments	Section 7.2.2 Exclusion Criteria, #7
Added current CDC guidance related to vaccination, which recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody treatment (eg, REGN10933+REGN10987) (CDC, 2020).	To provide current guidance regarding SARS-CoV-2 vaccination	Section 8.10.1 Prohibited and Permitted Medications

Description of Change	Brief Rationale	Section(s)
SARS-CoV-2 vaccinations will be recorded as a targeted concomitant medication.	To ensure collection of clinically relevant medical information	Section 9.2.3.3 Targeted Medication Review
Procedural details for virologic assessments were updated: • NP samples with an original result above the Upper Limit of Quantification (ULOQ) will be diluted for additional quantification testing. • Clarified that viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.	To provide quantification of viral load at higher levels, and to ensure current, accurate, and consistent information related to planned analyses	Section 9.2.5.1 Sample Collection for RT-qPCR Analysis Section 9.2.8.1 Virology
Patients hospitalized for ≤72 hours (for reasons other than COVID-19 illness but with current COVID-19 symptoms) will be eligible to participate in the study, if they also meet other eligibility criteria.	To assess the study drug in a broader patient population that may receive clinical benefit	Section 7.2.1 Inclusion Criteria, #3
The Schedule of Events footnotes were updated as follows: • Patients in cohort 1 enrolled after 691 patients in the cohort (including phase 1 patients) will follow the phase 2 schedule but will be considered enrolled in phase 3 • Pregnancy testing will be performed locally • Day 1 hematology, blood chemistry, and coagulation test samples will be collected prior to dosing (rather than randomization)	To provide operational clarity	Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Phase 1), #10 Section 9.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2), #5, 12
REGN10989 monotherapy will no longer be considered as part of this adaptive master protocol. References to REGN10989 have correspondingly been removed from the statistical analysis and related areas of the protocol.	Based on preclinical viral resistance data showing viral escape following monotherapy with anti-SARS-CoV-2 monoclonal antibodies, this study to assess combination therapies and will no longer include monotherapy arms.	Throughout the document
Emergency unblinding procedures were clarified, including manual unblinding in case of IWRS unavailability.	Per health authority request	Section 8.8 Emergency Unblinding
Updates to background information were made, including current authorizations and approvals for COVID-19 treatments and SARS-CoV-2 vaccines.	To ensure current, accurate, and consistent information	Section 1.5 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Hospitalized Patients with COVID-19 Section 3.2.1.3 Standard of Care Background Treatments
Other minor typographical corrections and updates were made.	To ensure document accuracy	Throughout the document

Amendment 5 EU

Description of Change	Brief Rationale	Section(s)
Per IDMC recommendation received on 30 October and 18 November 2020, patient enrollment in cohort 2 and cohort 3 has been placed on hold (pending IDMC review of further data on patients who are currently enrolled in these cohorts). Patient enrollment in cohort 1A and cohort 1 will continue. All currently enrolled patients will continue to follow the protocol schedule to which they were last consented.	Per IDMC recommendation based on a potential safety signal and an unfavorable risk-benefit profile in cohorts 2 and 3 at this time	Section 3.2.1.4 Patient Population and Study Cohorts Section 6.1 Study Description and Duration Section 6.1.1 Study Design Figure 3 Study Flow Diagram, Phase 2 Section 6.1.2 Study Duration Section 6.1.3 Description of Study Cohorts Section 6.3 Planned Interim Analysis Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria Section 8.6 Method of Treatment Assignment Section 9.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.2.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.4.3.1.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.4.3.2.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) Section 11.4.9 Control of Multiplicity Section 11.5 Interim Analysis
Risk-benefit language was updated.	To provide updated risk-benefit information for the program and considerations for a broader patient population	Section 3.3 Risk-Benefit
Study monitoring plan was updated to allow off-site/remote monitoring of study sites.	Per health authority request; to provide flexibility for site monitoring due to COVID-19	Section 12.2.1 Monitoring of Study Sites

Amendment 5

Description of Change	Brief Rationale	Section(s)
Study inclusion criteria was updated to extend COVID-19 symptom onset window from ≤7 days to ≤10 days prior to randomization.	To broaden patient eligibility and better align with the evolving epidemiology of when patients present to the hospital relative to COVID-19 symptom onset	Section 7.2.1 Inclusion Criteria, #4
Phase 2 target population was revised to include patients who have COVID-19 symptoms but are not requiring supplemental oxygen. Approximately 390 additional patients on room air will be enrolled in cohort 1A.	To enroll patients at earlier stages of the disease and enable broader assessment of treatment impact on viral burden and other measures	Section 3.2.1.4 Patient Population and Study Cohorts Section 3.2.1.5 Rationale for Primary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.1 Study Description and Duration Section 6.1.1 Study Design Study Duration Figure 3 Study Flow Diagram, Phase 2 Section 6.1.3 Description of Study Cohorts Section 7.1 Number of Patients Planned Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, #5 Section 7.2.2 Exclusion Criteria, #1 Table 2 Schedule of Events for Phase 2 Section 11.2.2 Phase 2 (Cohort 1A, Cohort 1, Cohort 2, Cohort 3) Section 11.4.3 Efficacy Analysis Section 11.4.4 Control of Multiplicity
In phase 2, day 7 and day 15 blood samples for hematology, blood chemistry, and coagulation tests were added for all patients. Additional blood samples for biomarker assessments will be collected at baseline (post-dose) and on days 7, 15, and 29.	To allow more comprehensive analysis of safety and efficacy, by including additional biomarkers associated with COVID-19, inflammation, and cardiac and/or other organ injury	Section 5.6 Pharmacodynamic and Other Biomarker Variables Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2), footnotes #2, #12 Section 9.2.8.8 Serum and Plasma for Cardiac Biomarkers (section added) Section19 References
At screening, diagnostic testing for SARS-CoV-2 infection will allow antigen tests in addition to molecular tests.	To provide operational flexibility	Section 7.2.1 Inclusion Criteria, #3 Table 1 Schedule of Events for Phase 1 (Part A and Part B) Table 2 Schedule of Events for Phase 2 Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Phase 2 interim analysis plans were updated. Sample size re-estimation language was removed.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 11.5 Interim Analysis
In phase 1, patients who have missing or negative baseline virologic sample(s) or are missing ≥1 follow-up virologic samples(s) will no longer be replaced.	No longer necessary to replace patients in phase 1, since phase 2 now includes extensive analyses of virologic efficacy	Section 7.4 Replacement of Patients

Description of Change	**Brief Rationale**	**Section(s)**
Information regarding appropriate high-altitude equivalents for sea-level oxygenation measurements was added.	To provide eligibility guidance to study sites in high-altitude areas	Section 7.2.1 Inclusion Criteria, #5 Section 7.2.2 Exclusion Criteria, #1 Appendix A Oxygenation Equivalence for Eligibility (appendix added)
Information regarding review of sentinel safety group (part A) was added.	To update safety information for the program	Section 3.2.1.1 Phase 1 Sentinel Safety Group
EudraCT number for the study was added; other minor editorial and administrative updates were made.	To ensure accuracy and consistency	Title page Section 1.1 Emergence of SARS CoV 2 and COVID 19 Section 3.2.1.1 Phase 1 Sentinel Safety Group Section 3.2.1.5 Rationale for Primary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 8.1 Investigational and Reference Treatments Section 9.1.3 Early Termination Section 9.2.8.4 Serological Immunoassays for Anti-SARS CoV 2 Antibodies Section 9.2.8.5 Serum and Plasma for Research Section 9.2.8.7 Cytokines References

Amendment 4

Description of Change	Brief Rationale	Section(s)
In phase 2, nasal swabs and saliva samples will no longer be collected. Only nasopharyngeal (NP) swabs will be collected in phase 2.	To allow adequate assessment of virologic efficacy, as NP swab is the current gold standard to detect SARS-CoV-2	Section 2.2 Secondary Objectives Section 4.2 Secondary Endpoints Figure 3 Study Flow Diagram, Phase 2 Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2), #7 (deleted) Section 9.2.5.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Sample Collection Section 11.4.3.2.2 Phase 2 (Cohort 1, Cohort 2, Cohort 3)
Phase 2 sample size has been increased to enable additional enrollment.	To allow adequate assessment of virologic efficacy	Section 6.1.1 Study Design Section 7.1 Number of Patients Planned Section 11.2.2 Phase 2 (Cohort 1, Cohort 2, and Cohort 3)
An additional secondary virologic efficacy endpoint has been added.	To allow adequate assessment of virologic efficacy	Section 4.2 Secondary Endpoints
Interim analysis plan has been updated to allow more flexible timing and for consistency throughout the protocol.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 11.5 Interim Analysis
A modified full analysis set (mFAS) was added and includes all randomized patients with a positive RT-qPCR for SARS-CoV-2 in NP swab at randomization.	To allow adequate assessment of virologic efficacy	Section 9.2.5.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Sample Collection Section 11.3.1 Efficacy Analysis Sets Section 11.4.1 Patient Disposition Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
In phase 2, hematology and coagulation tests will be performed at day 7 in patients who are hospitalized.	To allow assessment of relevant biomarkers	Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2), #2, #12
The following clarifications have been made to the Schedule of Events: • Clarified that at concomitant medications are continuously monitored in phase 1 and phase 2. • Removed incorrect vital sign assessments marked in dosing column in phase 2.	To improve clarity of study schedule	Table 1 Schedule of Events for Phase 1 (Part A and Part B) Table 2 Schedule of Events for Phase 2

Amendment 3

Description of Change	Brief Rationale	Section(s)
In phase 2, blood chemistry will be assessed at day 7 in patients who are hospitalized.	Per health authority request	Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2, footnote #13

Description of Change	Brief Rationale	Section(s)
Primary virologic efficacy in phase 2 will be assessed using nasopharyngeal (NP) swab samples. NP swab sample collection has been correspondingly added.	To allow adequate assessment of virologic efficacy	Section 2.2 Secondary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Table 2 Schedule of Events for Phase 2 Section 9.2.5.1 Saliva Sample, Nasal Swab, and Nasopharyngeal Swab Collection Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
Additional patients may be enrolled in phase 1 to replace patients who have missing or negative baseline virologic sample(s) or are missing ≥1 follow-up virologic sample(s).	To allow adequate assessment of virologic efficacy	Section 7.1 Number of Patients Planned Section 7.4 Replacement of Patients

Amendment 2

Description of Change	Brief Rationale	Section(s)
Grade 3 or 4 treatment-emergent AEs will be collected (phase 1 only)	Per health authority request	Section 3.2.1.5 Rationale for Primary Objectives Section 5.3 Safety Variables Section 6.1 Study Description and Duration Table 1 Schedule of Events for Phase 1 (Part A and B) Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Phase 1), #7 Section 9.1.4 Unscheduled Visits Section 10 Safety Evaluation and Reporting (and sub-sections therein)
Added day 57 collection of blood samples for safety laboratory testing (phase 1 only)	Per health authority request	Table 1 Schedule of Events for Phase 1 (Part A and B)
Clarified objective, endpoint, and procedure for assessing viral resistance	Per health authority request	Section 2.1 Exploratory Objectives Section 4.1 Exploratory Endpoints Section 9.2.8.1 Virology
Clarified EC and IC terminology related to dose rationale	To clarify in vitro data descriptions	Section 3.2.2 Rationale for Dose Selection
Added details to address controlling for type I error	Per health authority request	Section 11.4.4 Control of Multiplicity
Added ICU-associated secondary endpoints; other clarifications made to primary and secondary efficacy analysis and multiplicity control	To ensure consistency with planned statistical analysis	Section 4.2 Secondary Endpoints
Included secondary objective and endpoint to assess correlations in viral shedding across sample types	To understand differences in assessing virologic efficacy using distinct sampling sources	Section 2.2 Secondary Objectives Section 4.2 Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analysis

Description of Change	Brief Rationale	Section(s)
Added nasopharyngeal (NP) sampling to days 11 and 15 (phase 1 only)	To provide matching sample types across time points	Table 1 Schedule of Events for Phase 1 (Part A and B)
Study will be conducted in the US and other countries	To broaden the reach of study	Section 6.1 Study Description and Duration
Added country as a stratification factor for randomization in phase 2	To ensure balance in study populations	Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis
Screening for SARS-CoV-2 infection can be performed by any validated molecular diagnostic assay; historical record ≤72 hours of randomization is acceptable	To clarify acceptable screening criteria	Section 7.2.1 Inclusion Criteria, #3 Table 1 Schedule of Events for Phase 1 (Part A and B) Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Phase 1), #4 Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2), #4 Section 9.2.1.2 Molecular Diagnostic Test for SARS-CoV-2
For assessment of COVID-19 symptom onset during screening, symptoms are defined per investigator discretion	To clarify inclusion criterion	Section 7.2.1 Inclusion Criteria, #4
Updated study stopping criteria	To provide additional details for study stopping and/or adaptations	Section 6.1.4.2 Study Stopping Criteria
The Independent Data Monitoring Committee (IDMC) will review both safety and efficacy data during the study	To clarify the planned IDMC review process	Section 6.2.1 Independent Data Monitoring Committee
Any unused or leftover biological samples collected during the study may be used for exploratory research; maximum time period of allowable storage (for both exploratory research samples and pharmacogenomic samples) may be shorter per regional laws and regulations	To clarify the intended use and storage of samples	Section 9.2.6 Drug Concentration Measurements and Samples Section 9.2.7 Immunogenicity Measurements and Samples Section 9.2.8 Exploratory Pharmacodynamic/Biomarker Analyses Section 9.2.9 Pharmacogenomic Analysis (Optional)
The following operational changes have been made: • Phone visits have a window of ±1 day • Clarified that home-based visits may be done by home health staff	To provide additional flexibility for sample collection and assessments	Section 6.1 Study Description and Duration Table 1 Schedule of Events for Phase 1 (Part A and B) Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Phase 1), #2, #8 Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2), #2, #11
Specified parameters of early termination visit	To clarify early termination requirement for sample collection and assessments	Section 9.1.3 Early Termination from the Study
Added unscheduled visit	To provide a description of early termination visits	Section 9.1.4 Unscheduled Visits

Description of Change	Brief Rationale	Section(s)
Updated the list of targeted concomitant medications to be recorded	To ensure consistency with the eCRF	Section 9.2.3.3 Targeted Medication Review
Temperature will not be measured rectally	To clarify required assessments	Section 9.2.3.1.2 Body Temperature
Clarified a Statistical Plan in the Synopsis	To align to the main text	Synopsis: Statistical Plan
Simplified the Schedule of Events, and removed visit locations; visits may occur at any in-person location except where additional phone visits are indicated	To ensure clarity of study schedule and design	Section 6.1.2 Study Duration Table 1 Schedule of Events for Phase 1 (Part A and B) Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Phase 1) Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2 Schedule of Events (Phase 2)
Typographical, grammatical, editorial, and formatting updates	Implemented for clarity, accuracy, and consistency	Throughout the document

Amendment 1

Description of Change	Brief Rationale	Section(s)
Day 1 vital sign requirements (including pulse oximetry) added for patients in the phase 1 sentinel safety group	Per health authority request	Table 1 Schedule of Events for Phase 1 (Part A and Part B) Section 9.1.1.1 Footnotes for Table 1, footnote #7 Table 2 Schedule of Events for Phase 2 Section 9.1.2.1 Footnotes for Table 2, footnote #9
Independent Data Monitoring Committee (IDMC) description updated	Operational details to be provided in the IDMC charter	Section 6.2.1 Independent Data Monitoring Committee
Clarifications of study procedures	To improve clarity of procedures and planned analyses	Section 9.2 Study Procedures (and sub-sections therein)
Editorial updates implemented	To ensure clarity, accuracy, and consistency	Section 8.7 Blinding

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CK-MB	Creatine kinase-MB
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EC_{50}	In vitro neutralization potency
EC_{99}	Effective concentration of 99% viral neutralization
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EDC	Electronic data capture
ELF	Epithelial lining fluid
EMA	European Medicines Agency
EOS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	United States Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit

IDMC	Independent data monitoring committee
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MERS-CoV	Middle East respiratory syndrome coronavirus
mFAS	Modified full analysis set
NAb	Neutralizing antibody
NCI	National Cancer Institute
NLR	Neutrophil-lymphocyte ratio
NP	Nasopharyngeal
NT-proBNP	N-terminal pro B-type natriuretic peptide
OP	Oropharyngeal
PFU	Plaque forming unit
PGx	Pharmacogenomics
PK	Pharmacokinetic
PT	Preferred term
PT/INR	Prothrombin time
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
REGN10933+REGN10987	Co-administered REGN10933+REGN10987 combination therapy
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV	Severe acute respiratory syndrome coronavirus
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	Systems organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification

WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Hospitalized Patients with COVID-19
Site Locations	The study will be conducted in approximately 100 sites in the United States (US) and other countries. The long COVID sub-study will be conducted in approximately 5 sites in the US.
Principal Investigator	Eleftherios Mylonakis, MD, PhD

Objectives

Primary

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

The primary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

Phase 1/2 (Cohort 1)

The primary objective is to exclude futility of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

The safety and tolerability of REGN10933+REGN10987 compared to placebo will also be evaluated.

Phase 2 (Cohort 1A)

There is no primary objective for phase 2 cohort 1A as enrollment was prematurely terminated.

Phase 2 (Cohort 2 and Cohort 3)

There is no primary objective for cohort 2 and cohort 3 in phase 2 as enrollment was put on hold. All safety and efficacy analyses are exploratory.

Phase 3 (Cohort 1)

There is no primary objective for phase 3 cohort 1 as enrollment was prematurely terminated.

Secondary

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

The secondary objectives are:

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

Phase 1/2 (Cohort 1)

The key secondary objective is to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

The other secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate (descriptively) additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2 (Cohort 1A)

The secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2 (Cohort 2 and Cohort 3)

The secondary objectives are:

- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 3 (Cohort 1)

The secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

Phase 1/2/3 (Cohort 1)

The secondary objectives are:

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Study Design	This study is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the futility or efficacy, safety, and tolerability of REGN10933+REGN10987 in hospitalized adult patients with COVID-19.
Study Duration	The phase 1 portion of the study will last up to 170 days. The phase 2 portion of the study will last up to 58 days. The phase 3 portion of the study will last up to 58 days. For patients who join the long COVID sub-study, the study will last up to 181 days.
End of Study Definition	The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Target Population	The study population will consist of hospitalized adult patients with COVID-19, enrolled in 1 of 4 cohorts* based on disease severity at randomization: • **Cohort 1A**: With COVID-19 symptoms but not requiring supplemental oxygen

- **Cohort 1**: O2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device
- **Cohort 2***: On high-intensity oxygen therapy† but not on mechanical ventilation

  †High-intensity oxygen therapy is defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO2, or use of non-invasive ventilation to treat hypoxemia.
- **Cohort 3***: On mechanical ventilation

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

Sample Size

Overall, approximately 2252 patients were randomized in this study:

Phase 1

- **Cohort 1:** 60 patients

Phase 2

- **Cohort 1A:** 609 patients
- **Cohort 1:** 629 patients
- **Cohort 2:** 164 patients
- **Cohort 3:** 35 patients

Prematurely terminated phase 3

- **Cohort 1** (ie, patients randomized after 01 December 2020): 755 patients

Treatments

Phase 1, Phase 2, and Phase 3

- Co-administered REGN10933+REGN10987 combination therapy 2.4 g (1.2 g of REGN10933 plus 1.2 g of REGN10987) intravenously (IV) single dose
- Co-administered REGN10933+REGN10987 combination therapy 8.0 g (4.0 g of REGN10933 plus 4.0 g of REGN10987) IV single dose
- Placebo IV single dose

Endpoints

Primary

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

Virologic

The primary virologic endpoint is time-weighted average change from baseline viral load in NP sample through day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

Note: Time-weighted average of change from baseline in viral load from day 1 to day 7 will be calculated for each patient using the trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period.

Clinical

The primary clinical endpoint is the proportion of patients who died or went on mechanical ventilation from day 6 through day 29 and from day 1 through day 29.

Phase 1/2 (Cohort 1)

Futility

The primary endpoint is death or mechanical ventilation.

Safety and Tolerability

Safety and tolerability endpoints are as follows:

- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4

- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Phase 2 (Cohort 2 and Cohort 3)

There are no primary endpoints for cohort 2 and cohort 3 in phase 2.

Secondary **Phase 1/2 (Cohort 1)**

Clinical Efficacy

The key secondary endpoint is death or mechanical ventilation.

Other secondary endpoints include:

Virologic Efficacy

- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples

  Note: Time-weighted average of change from baseline in viral load from day 1 to day 7 will be calculated for each patient using the trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period.
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 11, as measured by RT-qPCR in NP swab samples
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to each post-baseline timepoint until day 29, as measured by RT-qPCR in NP swab samples
- Change from baseline in viral load at each post-baseline timepoint through day 29, as measured by RT-qPCR in NP swab samples
- Time to sustained negative RT-qPCR (negative RT-qPCR with no subsequent positive)

Clinical Efficacy

- All-cause death
- Mechanical ventilation
- Proportion of patients who died or went on mechanical ventilation by day 29
- Proportion of patients who died by day 29
- Proportion of patients who went on mechanical ventilation by day 29
- Time to discharge

PK/ADA

- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADA and (in phase 2 and phase 3 only) NAb to REGN10933 and REGN10987

Phase 3 (Cohort 1) and Phase 2 (Cohort 1A), Separately

The secondary endpoints include:

Virologic Efficacy

Endpoint	Timepoint	Population
Time-weighted average change from baseline viral load in NP sample	Through day 7	mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 7	Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	Seronegative mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	Baseline Viral load categories (>105, >106 copies/mL) mFAS
Time-weighted average change from baseline, change from baseline, and percent change from baseline in viral load in NP sample	Through each post-baseline timepoint until day 29	1. Seronegative mFAS, 2. Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS, 3. mFAS

Clinical Efficacy

- Proportion of patients who went on mechanical ventilation by day 29 (as applicable)
- Proportion of patients who died from day 6 to day 29 and from day 1 to day 29
- Proportion of patients who were discharged by day 29
- Proportion of patients who died or were readmitted to hospital over time
- Note: Readmission to hospital will be based on investigator report.
- Cumulative incidence of death over time (ie, overall survival)
- Cumulative incidence of mechanical ventilation over time (as applicable)
- Cumulative incidence of death or mechanical ventilation over time (as applicable)
- Time to discharge

Safety and Tolerability

- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADAs and NAbs to REGN10933 and REGN10987

Phase 2 (Cohort 2 and Cohort 3)

PK/ADA

- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADAs and NAbs to REGN10933 and REGN10987

Procedures and Assessments

Procedures and assessments will include the following:

Efficacy

- NP swabs for SARS-CoV-2 RT-qPCR
- Clinical and oxygen status

Safety and Tolerability

- Record treatment-emergent SAEs, treatment-emergent AESIs
- Blood collection for clinical laboratory evaluations
- Vital signs
- Procedure-related AEs (long COVID sub-study only)

Evaluation of Long COVID (Long COVID Sub-Study Only)

- Questionnaires to be administered by interviewers

Statistical Plan

Justification of Sample Size

Phase 3: Initial Estimation

The sample size for phase 3 was initially estimated to be 1350 patients (150 patients per arm across 3 treatment arms in 3 cohorts). Based on the new endpoint of death or mechanical ventilation, the sample size for phase 3 has been re-estimated to be 2505 patients in each of cohort 1 and cohort 1A.

The study was planned to continue enrolling additional patients seamlessly into the phase 3 portion of the study, until an adaptation decision on the dose(s), primary endpoint and final sample size for phase 3 is made based on the phase 2 data analysis. A total sample size of approximately 5010 patients was estimated for the phase 3 portion of the study (2505 per cohort, 835 per arm across 3 treatment arms in 2 cohorts). For cohort 1, a total of 241 events (estimated sample size of 2505 patients [835 patients

per arm]) would have been needed to provide 90% power at α=0.05 (2-sided) using a log-rank test to detect a risk reduction of 35.8% (ie, HR=0.642) in the cumulative incidence of patients who died or went on mechanical ventilation, assuming a 12.5% cumulative incidence rate in the placebo group by day 29.

Phase 3: Final Sample Size

Finalization of the sample size and patient population for phase 3 was planned to be subject to change and would be determined after review of phase 2 data. However, enrollment of patients into the study was terminated prematurely by the Sponsor on 09 April 2021 because of extremely slow enrollment in the months preceding the decision. The sample size of phase 3 was not re-estimated.

Approximately 2252 patients were randomized in the study, which includes 60 patients in phase 1 cohort 1, 629 in phase 2 cohort 1, 755 in planned phase 3 cohort 1, 609 in phase 2 cohort 1A, 164 in phase 2 cohort 2 and 35 in phase 2 cohort 3.

Assuming the proportion of patients who died or went on mechanical ventilation from day 1 to day 29 in placebo group is 13.1% which is same as the blinded proportion in the Seronegative mFAS patients of the pooled phase 3 cohort 1 and phase 2 cohort 1A and alpha is 0.05 2-sided, the minimal significant difference in relative risk reduction between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group is 29.0%, 41.2%, and 36.6% for overall mFAS, Seronegative mFAS, and High Viral Load mFAS patients, respectively.

Primary Efficacy Analysis

The efficacy analyses will be performed for the following patients on all efficacy endpoints, separately. The comparisons in all efficacy endpoints will be performed between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group as well as between each treatment group and placebo group.

- Pooled phase 3 cohort 1 and phase 2 cohort 1A patients
- Phase 3 cohort 1 patients (ie, patients randomized after 01 December 2020 in cohort 1)
- Phase 2 cohort 1A patients

Analysis of Primary Virologic Efficacy Endpoint

The primary analysis on the comparison between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo with respect to the virologic endpoint of time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 and other post-baseline visit timepoint will be performed in the Seronegative mFAS in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The estimand for the analysis is the difference in means between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Data collected after use of convalescent plasma therapy or other anti-spike monoclonals will be excluded from efficacy analysis. All other available data will be used in the analysis regardless of intercurrent events such as rescue medication or discontinuation, ie, treatment policy approach.

The analysis will be based on the observed data with no imputation for missing data except as defined in the SAP for viral load values that are below lower limit of detection (<LLOD), below lower limit of quantification (<LLOQ) or above upper limit of quantification (>ULOQ) of the assay.

The variable will be analyzed using the Analysis of Covariance (ANCOVA) model with treatment group and the type of background standard-of-care as fixed effects, and baseline viral load and treatment by baseline interaction as covariates.

The least squares means estimates for time-weighted average daily change from baseline in viral load for each treatment group, as well as the difference between the REGN10933+REGN10987 2.4g and 8.0g combined doses and placebo as well as between each individual dose treatment group and placebo, will be provided along with the corresponding two-sided p-value, standard error, and associated 95% confidence interval.

Analysis of Primary Clinical Efficacy Endpoints

The primary efficacy analysis will be the comparison between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The primary clinical endpoint will be analyzed using the landmark analysis approach for day 6 through day 29, as well as analyzed for day 1 through day 29 in the order specified in the statistical hierarchy.

	The proportion of patients who died or went on mechanical ventilation will be analyzed using either the exact method for binomial distribution or asymptotic normal approximation method. If the number of events is small (eg, $np \leq 5$ or $n(1-p) \leq 5$ in any treatment group, where n is the number of patients in the treatment group and p is the proportion of events), then the Fisher's exact test will be applied. Otherwise, stratified Cochran-Mantel Haenszel (CMH) test, stratified by the type of background standard-of-care (antiviral therapies and non-antiviral therapies), will be applied. Relative risk and relative risk reduction and corresponding 95% confidence intervals compared to placebo group will be estimated by Farrington-Manning method. Missing data will be considered as non-events. The analysis will be performed for the High Viral Load mFAS, the Seronegative mFAS, and the overall mFAS.
Exploratory Long COVID Analysis	Exploratory analyses related to long COVID will be summarized descriptively for all patients enrolled in the sub-study and may be reported separately from the CSR. Additional details will be provided in a separate long COVID statistical analysis plan (SAP) from the study SAP.
Safety Analysis	The analysis of safety data will be performed for cohort 1 in combined phases 1, 2 and 3, and phase 2 cohorts 1A, 2 and 3, separately in the FAS population. In this study, only targeted treatment-emergent adverse events will be recorded: • **All phases**: Treatment-emergent AESIs (grade ≥2 hypersensitivity and grade ≥2 IRRs) • **All phases, including long COVID sub-study**: Treatment-emergent SAEs • **Phase 1 only**: TEAEs (grade 3 or grade 4 only) • **Long COVID sub-study only**: positive SARS-CoV-2 local test result, from the day of consent to sub-study until day 180 The safety analysis will be based on the reported SAEs and AESIs and other safety information (clinical laboratory evaluations and vital signs). The summary of safety results will be presented for each treatment group. Subgroup analyses will be performed on efficacy endpoints and safety endpoints, as needed.

1. INTRODUCTION

1.1. Emergence of SARS-CoV-2 and COVID-19

Coronaviruses are a family of enveloped, single-stranded RNA viruses. In recent decades, 2 highly pathogenic strains of coronavirus were identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses were found to cause severe, and sometimes fatal, respiratory illness (Cui, 2019) (Fehr, 2015).

In December 2019, pneumonia of unknown cause was identified in clusters of patients in Wuhan City, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO, 2020) (Zhu, 2020). Millions of SARS-CoV-2 infections have been confirmed worldwide, and the rapidly-spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

1.2. Clinical Outcomes in Hospitalized Patients with COVID-19

Patients with COVID-19 are at risk for developing a variety of respiratory conditions, ranging from relatively mild respiratory symptoms to severe respiratory failure and death (Wu, 2020b). Among hospitalized patients, intensive care and/or oxygen supplementation (eg, mechanical ventilation) is often required, and reported fatality rates are high. In a report from the Chinese Center for Disease Control and Prevention that included 44,500 confirmed infections, nearly 20% of patients presented with advanced respiratory symptoms (14% with dyspnea, hypoxia, or >50% lung involvement on imaging; 5% with respiratory failure, shock, or multiorgan failure) (Wu, 2020b). Another analysis of patients with COVID-19 in China found that, among 1,099 hospitalized patients, 5% had been admitted to an intensive care unit (ICU), 2.3% required invasive mechanical ventilation, and 1.4% died. Among patients with advanced disease on admission (defined as pneumonia, hypoxemia, and tachypnea), these negative outcomes rose to 19%, 14.5%, and 8.1%, respectively (Guan, 2020). A report of 2634 hospitalized patients with COVID-19 in the United States identified similar clinical outcomes: 14.2% were admitted to an ICU, 12.2% required invasive mechanical ventilation, and 21% died (Richardson, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support (Chen, 2020) (Huang, 2020).

1.3. Long-Term Outcomes in Patients with COVID-19

Although much has been learned about acute SARS-CoV-2 infection and the resulting COVID-19 disease course, the long-term sequelae of SARS-CoV-2 infection and COVID-19 remain poorly understood. Long COVID is characterized by persistent symptoms, occurring beyond 4 weeks from the initial SARS-CoV-2 infection, that are not explained by an alternative diagnosis (Nalbandian, 2021) (CDC, 2021) (NICE, 2021). Initial assessments of long COVID indicate that approximately 10% to 35% of patients who recover from acute SARS-CoV-2 infection may experience persistent symptoms suggestive of long COVID (Tenforde, 2020) (Greenhalgh, 2020). To date, it is unclear whether and how the treatment of acute SARS-CoV-2 infection may impact the subsequent development of long COVID symptomatology.

1.4. The Role of Spike (S) Protein in SARS-CoV-2 Viral Pathogenesis

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein surrounded by an outer envelope. The envelope is comprised of membrane (M) protein and envelope (E) protein, which are involved in virus assembly, and spike (S) protein, which mediates entry into host cells. S proteins form large trimeric projections, providing the hallmark crown-like appearance of coronaviruses. S protein trimers bind to a host receptor and, after priming by cellular proteases, mediate host–virus membrane fusion (Li, 2016). S protein appears to be central to viral infectivity by SARS-CoV-2. SARS-CoV-2 S protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) with high affinity, and in cell assays and animal models can utilize ACE2 as a functional receptor for host cell entry (Ou, 2020) (Hoffmann, 2020) (Walls, 2020).

Blockade of host cell entry through the use of neutralizing antibodies against S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of S protein in the pathogenesis of SARS-CoV-2, a number of efforts are underway to develop antibodies and vaccines that target this protein.

1.5. REGN10933+REGN10987: Human Monoclonal Antibodies Against SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc. (Regeneron) has developed monoclonal antibodies (mAbs) directed against the RBD of the SARS-CoV-2 S protein. Casirivimab (REGN10933) and imdevimab (REGN10987) are human, IgG1 mAbs that bind simultaneously to the RBD and block interaction with ACE2. As co-administered combination therapy, casirivimab and imdevimab, also referred to by the proprietary name conditionally accepted by the FDA (REGEN-COV™) and by the EMA (RONPAPREVE®), is being evaluated for the treatment and prevention of SARS-CoV-2 infection and retains neutralization potency against circulating SARS-CoV-2 variants of concern (UK B.1.1.7 [alpha], South Africa B.1.351 [beta], California B.1.429 [epsilon], India B.1.617.2 [delta], and Brazil P.1 [gamma]) and protects against the selection of resistant variants in vitro (Copin, 2021) (REGEN-COV™ (casirivimab with imdevimab) [HCP Fact Sheet], 2021).

In phase 3 clinical trials, the combination of casirivimab and imdevimab was shown to be effective and well-tolerated in the treatment of outpatient and hospitalized adults with COVID-19, and in the prevention of SARS-CoV-2 infection in adults and adolescents (Horby, 2021) (O'Brien, 2021a) (O'Brien, 2021b) (Weinreich, 2021b).

1.6. A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Hospitalized Patients with COVID-19

Several therapeutic and preventative agents are under investigation for the treatment or prevention of COVID-19. While a number of these agents have received approvals or conditional authorizations (FDA, 2021) (EMA, 2021), there remains a significant unmet medical need for COVID-19 treatments in the hospitalized setting. This study is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the futility or efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") in hospitalized adult patients with COVID-19.

Note: On 09 April 2021, the Sponsor made a business decision to terminate patient enrollment in this study due to low recruitment rates. Patients who had been enrolled will continue to be followed up according to the Schedule of Events (Section 9.1). In addition, enrolled patients at select sites

may be reconsented to protocol amendment 8 US and followed in an exploratory sub-study for an extended period to monitor for symptoms of long COVID.

For more information regarding the rationale for the study design, see Section 3.2.1. Additional background information on the study drugs and the overall development program can be found in the Investigator's Brochure(s).

2. STUDY OBJECTIVES

2.1. Primary Objectives

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

The primary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

Phase 1/2 (Cohort 1)

The primary objective is to exclude futility of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

The safety and tolerability of REGN10933+REGN10987 compared to placebo will also be evaluated.

Phase 2 (Cohort 1A)

There is no primary objective for phase 2 cohort 1A as enrollment was prematurely terminated.

Phase 2 (Cohort 2 and Cohort 3)

There is no primary objective for cohort 2 and cohort 3 in phase 2 as enrollment was put on hold. All safety and efficacy analyses are exploratory.

Phase 3 (Cohort 1)

There is no primary objective for phase 3 cohort 1 as enrollment was prematurely terminated.

2.2. Secondary Objectives

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

The secondary objectives are:

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

Phase 1/2 (Cohort 1)

The key secondary objective is to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

The other secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate (descriptively) additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2 (Cohort 1A)

The secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2 (Cohort 2 and Cohort 3)

The secondary objectives are:

- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 3 (Cohort 1)

The secondary objectives are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

Phase 1/2/3 (Cohort 1)

The secondary objectives are:

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

2.3. Exploratory Objectives

The exploratory objectives of all phases of the study are:

- To assess viral genetic variation in patients with a positive SARS-CoV-2 RT-qPCR
- To explore the potential association of baseline humoral immune response to SARS-CoV-2 on response to REGN10933+REGN10987
- To evaluate the effects of REGN10933+REGN10987 compared to placebo on generation of a humoral immune response to SARS-CoV-2 (as measured by anti-SARS-CoV-2 N protein)
- To explore the effects of REGN10933+REGN10987 on measures of SARS-CoV-2 infectivity as assessed in experimental laboratory assays
- To explore biomarkers predictive of REGN10933+REGN10987 and safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To understand the underlying mechanisms of action and biology of REGN10933+REGN10987, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers

For phase 2 (cohort 2 and cohort 3), the exploratory objectives include:

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation (as applicable based on the cohort)
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo

For phase 2 cohort 1a and phase 3 cohort 1, an additional exploratory objective is to evaluate the impact of REGN10933+REGN10987 treatment, given during acute SARS-CoV-2 infection, on long COVID symptoms (long COVID sub-study)

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Treatment of hospitalized patients with COVID-19 with REGN10933+REGN10987 will improve clinical outcomes, be tolerated, and reduce viral load.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

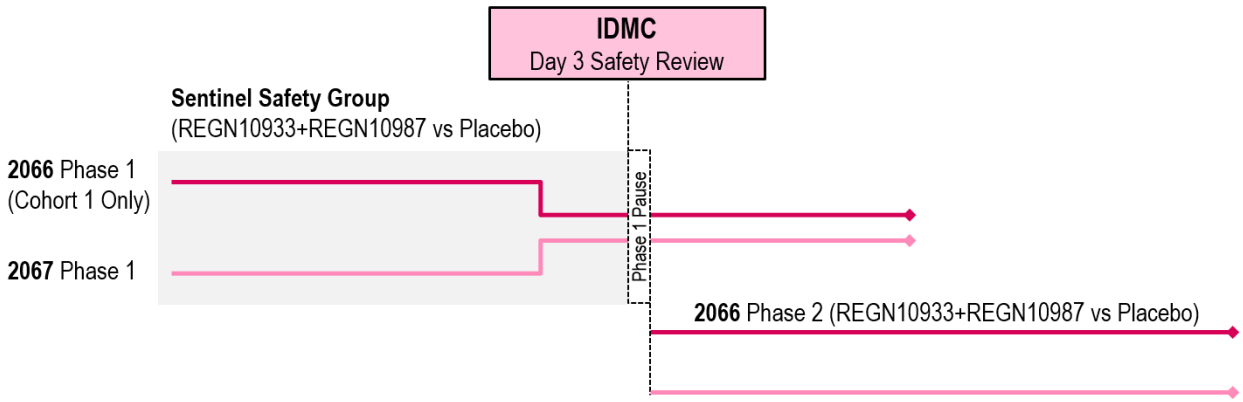
This randomized, double-blinded, placebo-controlled, adaptive phase 1/2/3 master protocol will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in hospitalized patients with COVID-19. The multicenter conduct of this study will enable generalizable evidence of the safety, tolerability, and efficacy of these investigational mAbs for COVID-19.

3.2.1.1. Phase 1 Sentinel Safety Group

This master protocol will include a first-in-human (FIH) phase 1 study to evaluate safety and tolerability. Driven by the medical urgency of the COVID-19 pandemic, the process described below is designed to maximize efficient enrollment of eligible patients while optimizing safety of FIH exposure with limited preclinical data (see Section 3.3).

Phase 1 will include a sentinel safety group, where the initial safety data up to day 3 will be reviewed by an independent data monitoring committee (IDMC).

Figure 1: Phase 1 Sentinel Safety Group



Patients in this sentinel safety group can be derived from either of 2 concurrent FIH studies, where the safety and tolerability of REGN10933+REGN10987 will be evaluated:

- R10933-10987-COV-2066, in hospitalized adult patients with COVID-19

- R10933-10987-COV-2067, in adult outpatients with COVID-19

For IDMC review, patients will be pooled together from the phase 1 portions of either of the 2 studies. Once safety data have been collected on day 3 for approximately 30 patients (from one or both of the studies combined), the IDMC will review the data.

Note that phase 1 enrollment will pause during the IDMC review.

Initiation of phase 2 enrollment is contingent upon IDMC review of phase 1 data from the sentinel safety group. Study stopping criteria are outlined in Section 6.1.4.2.

After IDMC reviews and provides a positive recommendation for the phase sentinel safety group, enrollment of studies assessing REGN10933+REGN10987 (including REGN10933+REGN10987 treatment arms in phase 2 of this study and R10933-10987-COV-2067) may begin.

Once phase 2 of this study is active, phase 1 will continue to enroll to completion. However, phase 2 enrollment does not require the completion of phase 1 enrollment.

Patient Population in the Phase 1 Sentinel Safety Group

In this study, only patients from cohort 1 will be included in the sentinel safety group. Patients from cohort 2 and cohort 3 will not be included. Due to the advanced nature of their illness and confounding adverse events related to underlying COVID-19, assessing the FIH safety of the anti-SARS-CoV-2 S protein mAbs will be challenging in cohort 2 and cohort 3 patients.

Review of Sentinel Safety Group, Part A (Information Added to Protocol in Amendment 5)

A blinded Sponsor analysis of the sentinel safety group data showed that REGN10933+REGN10987 was well tolerated in hospitalized or ambulatory patients with COVID-19, with no hypersensitivity reactions or infusion-related reactions reported. Vital signs and laboratory assessments did not identify any safety signals. IDMC review recommended to continue enrollment in the studies after unblinded data review. For more details, refer to the Investigator's Brochure.

3.2.1.2. Adaptive Master Protocol Design

The study utilizes an adaptive master protocol design. The adaptive design has been selected to maximize the efficiency of identifying early signs of efficacy, increase the efficiency of studying multiple therapeutic combinations, and avoid the use of ineffective dose levels in patients with COVID-19.

Due to the novel nature of the COVID-19 pandemic, efficacy endpoints are not well established, and the standard-of-care is expected to evolve over time. The adaptive design of this study allows for the assessment of virologic and clinical efficacy endpoints in phase 2, which are then seamlessly confirmed in the phase 3 portion of the study, as well as evaluating the benefit risk of the different treatment arms.

This master protocol will allow for treatment arm(s) to be dropped if there is a clinically meaningful imbalance between treatment arms in the incidence of SAEs or the incidence of AESIs, or if there is a meaningful imbalance between treatment arms regarding efficacy endpoints.

The design will allow for the addition of new treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing (umbrella design), refinement of disease

characteristics of eligible study populations (basket design), as well as other multiple adaptations, including dropping of a treatment arm, determination of phase 3 primary endpoints, and phase 3 sample size estimation.

3.2.1.3. Standard-of-Care Background Treatments

Several putative COVID-19 treatments are currently under investigation and in some cases have been authorized, approved or allowed for compounding for use in hospitalized patients, including remdesivir, convalescent plasma, and dexamethasone (refer to Section 1.6). Some of these products may be used as standard-of-care. Although there are some exceptions for treatments which may confound the effectiveness of the study drug, such as convalescent plasma (refer to Section 7.2.2 for exclusion criteria), the study design is generally flexible on the types of putative treatments used in the hospitalized setting for background standard-of-care.

This study will compare REGN10933+REGN10987 to placebo, all given in addition to the local standard-of-care. Since the standard-of-care for COVID-19 is evolving and will vary across sites and regions, randomization will be stratified based on the type of background standard-of-care: antiviral therapies and non-antiviral therapies as described in Section 8.6. Including this as a stratification factor will ensure an appropriate balance in treatment assignment across the different types of standard-of-care and allow evaluation of efficacy based on background treatments given.

3.2.1.4. Patient Population and Study Cohorts

There is some evidence that suggests baseline disease severity influences progression and outcomes of COVID19. In order to evaluate potential differential treatment effects across the spectrum of hospitalized COVID-19 patients, the study will be conducted and analyzed in 4 cohorts* of hospitalized adult patients with COVID-19 that require varying degrees of oxygen support at randomization:

- **Cohort 1A:** With COVID-19 symptoms but not requiring supplemental oxygen
- **Cohort 1**: Patients on low-flow oxygen supplementation
- **Cohort 2***: Patients requiring high-intensity oxygen therapy but not on mechanical ventilation
- **Cohort 3***: Patients requiring mechanical ventilation

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

See Section 6.1.3 for further details on the study cohort definitions.

3.2.1.5. Rationale for Primary Objectives

Safety and Tolerability

The primary objectives of phase 1 and phase 2 include safety and tolerability, evaluated by targeted collection of treatment-emergent serious adverse events (SAEs) throughout the study and treatment-emergent adverse events of special interest (AESIs) through day 29. In addition, grade 3 and grade 4 treatment-emergent adverse events (TEAEs) will be recorded to inform safety assessments in later phases of the study.

The study population of hospitalized adult patients with COVID-19 will have a complicated disease presentation at baseline that could quickly and unexpectedly deteriorate and progress. As such, their TEAE profile will be complex and dynamic. Mainly due to their underlying disease, TEAEs are expected to progress or improve in severity and seriousness multiple times throughout the study. Accurately collecting such a large volume of TEAEs could impose unnecessary burden on an already over-strained healthcare system and frequent exposure to infected patients could increase the risk of infection to the study staff.

Evaluating targeted grade 3 or 4 TEAEs, treatment-emergent SAEs, and treatment-emergent AESIs (grade ≥2 hypersensitivity reactions and grade ≥2 infusion-related reactions) will provide the most relevant safety information to adequately evaluate the safety and tolerability of REGN10933+REGN10987. This subset of grade 3 or 4 TEAEs, treatment-emergent SAEs, and treatment-emergent AESIs encompasses the key safety concern that would be expected for mAbs against exogenous targets and help evaluate unexpected SAEs. Regeneron plans to collect data on non-serious TEAEs (as well as serious TEAEs) in a parallel-conducted prophylaxis study (R10933-10987-COV-2069) and a repeated dose study in adult volunteers (R10933-10987-HV-2093) with REGN10933+REGN10987, where the study population will not have a complicated disease presentation and there is a significantly lower risk of overburdening the health care delivery system.

Clinical Efficacy

The REGN10933+REGN10987 mAb combination therapy was created as a potential anti-viral treatment and (and as combination to prevent viral escape mutants during treatment). The prospective hypothesis is that REGN10933+REGN10987 is intended to substitute for the endogenous immune response, that this endogenous response might be delayed or inadequate in some patients (eg, patients who are seronegative at baseline) and that REGN10933+REGN10987 might be expected to have most benefit in these seronegative patients who are still positive at baseline for the presence of virus in NP swabs based on a quantitative PCR test. Phase 1/2 data from the Sponsor's parallel study in outpatients with COVID-19 (R10933-10987-COV-2067) prospectively validated these concepts (for both anti-viral activity and clinical benefit). R10933-10987-COV-2067also showed that high viral titer at baseline in outpatients is highly correlated with a seronegative status at baseline. However, some patients who were seropositive at baseline had poor outcomes, suggesting that the serologic response in some patients may not be of sufficient quality to suppress viral replication. Based on these data, it is hypothesized for the current study that clinical benefit in hospitalized patients may be greatest in patients who are still positive at baseline for the presence of virus in NP swabs based on a quantitative PCR test and seronegative and/or in patients with high viral load regardless of serologic status.

The clinical efficacy endpoint that will be assessed is mechanical ventilation or death. This is a change from the endpoint initially planned for the study: a 7-point ordinal scale (rating clinical status from death [1] to not hospitalized [7]) used to assess changes in clinical status (see Section 9.2.5.2.4). Emerging insights show that the 7-point ordinal scale can be highly variable, particularly with respect to oxygen requirements as it depends heavily on the clinical judgement of the clinician. This variability makes it far less optimal for assessment of treatment effects, especially in relatively small sample sizes. As such, the primary clinical efficacy assessment for phase 1/2 has been changed to focus on mechanical ventilation or death, objective measures that are clinically meaningful and representative of the most severe clinical manifestations of COVID-

19. Preventing patients from going on mechanical ventilation or from dying is a highly relevant clinical outcome and one that will be simpler for patients and providers to understand compared to the previously proposed endpoint of change in ordinal scale.

The phase 1/2 analysis of cohort 1 will focus first on excluding futility and then to assess clinical efficacy of REGN10933+REGN10987 on death or mechanical ventilation (see Section 11.4.9). An initial evaluation of futility will be performed to understand if there is a low probability of achieving statistical significance for the primary endpoint of mechanical ventilation or death. If the study as designed is determined not to be futile, subsequent assessments of efficacy will be performed hierarchically in populations mostly likely to benefit from a potent anti-viral – patients that have not mounted an efficient immune response, ie, those that are seronegative or with high viral load at baseline. Additional secondary endpoints will be assessed descriptively, including in other sets of patients (eg, positive at baseline for the presence of virus in NP swabs based on a quantitative PCR test and positive, positive at baseline for the presence of virus in NP swabs based on a quantitative PCR test and regardless of serologic status). If the study as designed is determined to be futile, all analyses of clinical endpoints will be descriptive and plans for phase 3 will be reconsidered.

Demonstration of a convincing benefit in patients who are seronegative and/or have high viral loads at baseline, and at least a neutral effect in other subsets of patients, would support REGN10933+REGN10987 being used in either a targeted fashion based on point of care testing that is now available in many hospitals, or possibly in the overall COVID-19 population depending on the specific results.

Virologic Efficacy

The primary mechanism of action of REGN10933+REGN10987 is blockade of the S protein RBD interaction with ACE2, leading to decreased infection of host cells. Blocking viral entry would result in reductions in SARS-CoV-2 RNA replication, and corresponding viral load in affected tissues. In phase 1 and phase 2, the primary virologic endpoint will therefore evaluate, as proof of mechanism, the ability of REGN10933+REGN10987 to reduce viral load in the upper respiratory tract. day 22 (21 days after dosing) was initially chosen as the cutoff date for this analysis, based on accumulating evidence that this time period approaches the lower limit of detection in samples collected from the upper respiratory tract in patients spontaneously recovering from COVID-19 (He, 2020) (Cao, 2020) (Wang, 2020b).

Subsequently, the result of a phase 1/2 analysis in R10933-10987-COV-2067 (outpatients) showed that the majority of viral clearance had occurred prior to day 7 (Weinreich, 2020), suggesting that analysis at earlier timepoints may also be of value in assessing virologic efficacy.

3.2.1.6. Rationale for Final Analysis of the Study

On 30 October 2020, an Independent Data Monitoring Committee (IDMC) recommended pausing enrollment into cohort 2 and cohort 3 based on a potential safety imbalance, while proceeding with enrollment in cohort 1A and cohort 1. All cohort 2 and 3 patients enrolled at the time of the recommendation continued in the study and were followed up through the end of study visit as per the protocol. This IDMC recommendation on enrollment was maintained for the duration of the study.

An unblinded phase 1/2 analysis was performed on the patients who were randomized through 01 December 2020 in phase 1 (cohort 1 only) and phase 2 (cohorts 1, 2, and 3) using a data cutoff date of 09 December 2020, based on a database lock on 22 December 2020 (refer to the phase 1/2 SAP dated 21 December 2020 for details). Phase 2 cohort 1A was not included in the analysis. All patients enrolled into cohort 1 after 01 December 2020 were considered to be part of phase 3.

On 09 April 2021, the Sponsor made a business decision to terminate patient enrollment in this study due to extremely low recruitment over several months. This decision was not based on any safety concerns. Accordingly, phase 3 cohort 1 and phase 2 cohort 1A enrollment was prematurely terminated. Until this time, only cohort 1 patients were enrolled into the phase 3 portion of the study. All ongoing subjects were followed up through their end of study visit as per the protocol.

Cohort 1 reached its phase 2 enrollment goal first, and phase 3 cohort 1 started enrollment after 01 December 2020. As cohort 1A never reached its predetermined phase 2 enrollment goal of 1000 patients, phase 2 cohort 1A and cohort 1 enrolled concurrently (refer to Section 7.1 for the number of patients enrolled in each phase by cohort). Phase 2 cohort 1A data were handled and overseen similar to phase 3 cohort 1 data.

Given much smaller sample size than anticipated as a result of early termination of enrollment, the Sponsor has elected to pool phase 2 cohort 1A and phase 3 cohort 1 and combine the REGN10933+REGN10987 2.4g and 8.0g dose groups for the primary analyses. Analyses of each cohort alone and each dose alone will be descriptive and considered secondary.

3.2.1.7. Long COVID Sub-Study

Long COVID encompasses a wide variety of heterogeneous neurological, neuropsychiatric, autonomic, and systemic symptoms, including fatigue, cognitive difficulties, mood dysregulation, dyspnea, coughing, palpitations, chest pain, fever, and joint or muscle pain) and can be debilitating (Alwan, 2020) (del Rio, 2020). However, the clusters of symptoms reported by patients post-COVID-19 are not unique or specific to long COVID, and for most of the symptoms there are no validated biomarkers for diagnosis of long COVID, with identification of long COVID largely constrained in medical practice to diagnostic exclusion (Burke, 2021).

To address knowledge gaps in the etiology and symptomatology of long COVID, additional assessments will be conducted as a sub-study at select sites. These assessments will evaluate patient-reported symptoms and related outcomes, to develop a better understanding of the nature of long COVID and to assess whether prior treatment with REGN10933+REGN10987 during acute SARS-CoV-2 infection may impact subsequent symptoms and quality-of-life outcomes. In addition, blood samples will be collected for biomarker analysis and immunoprofiling, to gain a better understanding of the underlying biology of long COVID and the impact of prior treatment in the acute stage of disease. Nasopharyngeal (NP) swab samples will be collected to assess for the presence of SARS-CoV-2 during this later stage of analysis.

Patient-Reported Symptoms. To better understand the patient experience of long COVID, patients will answer questions about their symptoms and how these symptoms impact their functioning and quality of life (Section 9.2.9.1). The analysis will largely focus on pre-defined groupings of symptoms identified across guidelines from the Centers for Disease Control (CDC), National Health Service (NHS), and the World Health Organization (WHO) (CDC, 2021) (NHS, 2021) (WHO, 2021). Symptoms will be analyzed according to whether they are considered

lingering symptoms and identified across all three guidelines (category A, identified across all three guidelines (category B), or identified across at least two guidelines (category C) (Section 4.3 Table 4). In addition to these areas of focus, a variety of concepts important to patients beyond symptoms will be evaluated, including functioning, impact on daily lives, and overall quality of life, in order to generate a broad depiction of long COVID in the study population.

Blood sample collection. While the underlying biology of long COVID is unclear, potential mechanisms contributing to the pathophysiology of post-acute COVID-19 disease include virus-specific pathophysiologic changes, immunologic aberrations and inflammatory damage in response to acute infection, and expected sequelae of post-critical illness (Nalbandian, 2021) (Talla, 2021). Based on these data, as well as reports of biomarkers and signatures observed in patients with long COVID (Nalbandian, 2021), an agnostic multiplex proteomic and transcriptomic profiling focused on the disease mechanism will be performed to gather additional insights in the sequelae of long COVID. The specific aims of this analysis are described in Section 9.2.9.2.

3.2.2. Rationale for Dose Selection

This study will assess a single IV dose of REGN10933+REGN10987 as combination therapy in a 1:1 ratio. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are non-competing mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure[s]). The study will evaluate the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2.4 g (1.2 g per mAb), which is expected to be an efficacious dose (see below). The study will also evaluate REGN10933+REGN10987 at a higher dose, 8.0 g (4.0 g per mAb), in the event that a higher dose is required for efficacy.

Cellular entry of coronaviruses depends on binding of the S protein to a specific cellular receptor and subsequent S protein priming by cellular proteases. ACE2 is the receptor for cellular entry of SARS-CoV-2 and its gene expression has been reported in the lungs, particularly in type-2 alveolar epithelial cells and bronchial airway epithelium (Wu, 2020a) (Xu, 2020) (Zhao, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration of 99% viral neutralization (EC_{99})* observed against live virus SARS-CoV-2 and to then identify a dose that will meet or exceed this concentration in lung ELF. The EC_{99} against SARS-CoV-2 is 0.14 µg/mL (REGN10933) and 0.78 µg/mL (REGN10987).

An average lung ELF-to-serum mean C_{max} ratio of ~0.15 has been reported for other exogenous IgG1 mAbs for the treatment of *Staphylococcus aureus* lung infections (Magyarics, 2019). It is assumed that the lung ELF-to-serum C_{max} ratio is 0.15 for REGN10933 and REGN10987. Dividing the target lung ELF concentration by this ratio, the associated serum concentration for these targets is therefore estimated to be ~at least 5 µg/mL for the combination of REGN10987+REGN10933.

Taking into account uncertainties regarding mAb penetration into lung ELF, prediction of human PK, and effects of disease on PK, 20 µg/mL was selected as a target concentration in serum for the initial dose of REGN10933+REGN10987 combination therapy. The goal for the initial REGN10933+REGN10987 combination dose is for ≥95% of patients to exceed the target serum concentration for 28 days after dosing, for each mAb. Based on healthy subject human PK data for

six Regeneron mAbs directed against an exogenous target (N=6 to 12 subjects per mAb), a single IV combination dose of 1.2 g per mAb is predicted to result in ≥95% of patients exceeding the target serum concentration for 28 days after dosing, for each mAb.

*Please note that the EC values discussed here are identical to the inhibitory concentration (IC) values discussed in the Investigator's Brochure(s).

3.3. Risk-Benefit

The anticipated risks and benefits of REGN10933+REGN10987 (casirivimab+imdevimab) are informed by preclinical and clinical data, including data from phase 3 trials.

For additional information concerning clinical and preclinical data, refer to the Investigator's Brochure.

3.3.1. Summary of Efficacy and Safety Profile in Clinical Trials

Clinical trial data are summarized below. Overall, REGN10933+REGN10987 have demonstrated efficacy as an anti-viral agent for the treatment and prevention of COVID-19, across a variety of populations, and is generally well-tolerated with an acceptable safety profile.

Clinical Benefit of REGN10933+REGN10987 in Clinical Trials for the Treatment of COVID-19. In COV-2067, the phase 3 outpatient treatment trial, a single IV dose of REGN10933+REGN10987 was shown (relative to placebo) to reduce COVID-19-related hospitalizations or all-cause death by 71.3% (2400 mg dose) and 70.4% (1200 mg dose), reduce symptom duration by 4 days (2400 mg and 1200 mg), and reduce viral load over the first 7 days. Serious adverse events occurred more frequently in the placebo group (4.0%) than in either treatment group (2400 mg, 1.1%; 1200 mg, 1.3%), and grade ≥2 infusion-related reactions were infrequent (<0.3% in all groups) (Weinreich, 2021b). Similar virologic efficacy and a similar safety profile were observed in the phase 1/2 portion of this trial, which evaluated REGN10933+REGN10987 at 8000 mg and 2400 mg IV doses (Weinreich, 2021a).

Clinical Benefit of REGN10933+REGN10987 in Clinical Trials for the Prevention of COVID-19. In COV-2069, the phase 3 prevention trial in those at high risk of infection by a household contact, a single subcutaneous (SC) dose of REGN10933+REGN10987 (1200 mg) reduced (relative to placebo) symptomatic SARS-CoV-2 infection by 81.4%, and reduced overall SARS-CoV-2 infection by 66.4%. Serious adverse events occurred at similar frequencies in the treatment group (1%) and placebo group (1%). Injection-site reactions were more common in the treatment group (4%) compared to the placebo group (2%), but no injection-site reactions in the study were grade 3 or above. The majority of injection site reactions occurred within 1 day and resolved within 2 days (O'Brien, 2021b).

Among a sub-group of individuals in COV-2069 who were identified as SARS-CoV-2 positive but asymptomatic during screening, a single SC dose of casirivimab and imdevimab (1200 mg) reduced (relative to placebo) progression to symptomatic disease by 31.5%, and reduced the duration of symptoms in those that developed symptomatic infections. Injection-site reactions were more common in the treatment group (4%) compared to the placebo group (1%), but no injection-site reactions in the study were grade 3 or above (O'Brien, 2021a).

In COV-2069, efficacy results were similar in adolescents (age 12 to <18) as observed in adults: 0% of subjects in the 1200 mg SC treatment group experienced symptomatic infection, compared

with 9.3% of subjects in the placebo group. Safety data in adolescent subjects were also similar to that observed in adults. Injection site reactions were more common in the treatment group (5.9%) compared to the placebo group (1.6%), but none were grade 3 or above in any group.

In COV-2093, the adult volunteer study evaluating multiple doses of SC administration of REGN10933+REGN10987 (monthly dosing over 6 months), exploratory efficacy results showed benefit with chronic treatment for preventing COVID-19. This efficacy was balanced by an acceptable safety profile, where injection site reactions were more common in the treatment group (34.6%) compared with the placebo group (15.8%), but none were grade 3 or above in any group and all injection site reactions were either self-limiting or manageable with over-the-counter medications.

3.3.2. Summary of Risks

Important Identified Risks. As with other protein therapeutics, hypersensitivity reactions, including acute infusion-related reactions (IV administration) or injection site reactions (SC administration), may develop immediately or within a few hours to days after study drug administration. Hypersensitivity reactions, including anaphylaxis, infusion-related reactions or injection site reactions, have been observed in patients who received REGN10933+REGN10987 during ongoing clinical trials.

Important Potential Risks. The important potential risks of REGN10933+REGN10987 are the clinical consequences of immunogenicity and embryo-fetal toxicity.

Protein therapeutics carry the potential risk of an immunogenic response in the form of anti-drug antibody (ADA) and NAb development following administration, with possible consequences on safety and efficacy. Therefore, blood samples for immunogenicity assessment will be collected during the studies.

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier and are present in breast milk; therefore, the REGN10933+REGN10987 combination therapy have the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of REGN10933 and REGN10987, off-target pharmacological effects are not anticipated in either the mother or the fetus, and no off-target binding of REGN10933 or REGN10987 was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However, it is unknown whether the potential transfer of the combination of REGN10933+REGN10987 therapy provides any treatment benefit or risk to the developing fetus or a breastfed child.

There is currently limited clinical experience in the use of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy in female patients who are pregnant or breastfeeding. The combination of REGN10933+REGN10987 therapy should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors. If a female patient is pregnant or were to become pregnant while receiving REGN10933+REGN10987 combination, the pregnancy should be followed until outcome and any safety issue observed get reported.

Other Theoretical Considerations. Theoretical risks of administration of the REGN10933+REGN10987 combination include interference with the patient's endogenous immune response to either SARS-CoV-2 infection or vaccination against COVID-19. In this study, risk mitigation includes exclusion criteria for certain vaccination scenarios (refer to Section 7.2.2). A reference to current CDC guidance is provided (Section 8.10.1) to aid investigators on appropriate management of COVID-19 vaccination.

Antibody-dependent enhancement (ADE) has been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances Fc gamma receptor (FcγR)-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). REGN10933 and REGN10987 retain the Fc region, as this may play a role in protecting against viral infection (Yasui, 2014), there is no strong evidence of ADE in other coronavirus models (Kam, 2007) (Liu, 2019) (Luo, 2018). To date, Fc-containing mAbs developed by the Sponsor for Ebola virus and MERS-CoV have demonstrated specificity to their exogenous targets with no significant unexpected safety findings in preclinical or clinical studies. All patients will have follow-up assessments by phone during the drug elimination period.

Pediatric Population. Emerging data suggest that the pediatric population is equally vulnerable to SARS-COV-2 infection, and may contribute significantly to viral transmission (Wang, 2016) (Weingartl, 2004). Moreover, neonatal transmission of SARS CoV-2 has also been reported, suggesting that the youngest of the pediatric population can also be at risk of infection (Lewis, 2020) (Szablewski, 2020). If infected, the burden of severe disease in pediatric patients that become symptomatic and develop COVID-19 seem to be greater in those with underlying medical conditions. REGN10933+REGN10987 was safe and well-tolerated in the adult population and no new safety signals were identified in the adolescent population (>12 years). As it is an exogenous target, the safety of REGN10933+REGN10987 is not anticipated to be different from that observed in the adult patients. Additionally, nonclinical toxicology studies have not shown any safety findings including no tissue cross-reactivity to human fetal tissues. These data therefore favor assessing the safety and efficacy of REGN10933+REGN10987 in pediatric patients (for more information on dose rationale for these patients, refer to Section 3.2.1.6).

Summary. Overall, the anticipated benefit of REGN10933+REGN10987 combination therapy in treatment of infection with SARS-CoV-2 virus, along with the risk minimization measures in place, support continued clinical development of the product.

4. ENDPOINTS

Endpoints are specified for each study cohort (as defined in Section 6.1.3).

4.1. Primary Endpoints

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

Virologic

The primary virologic endpoint is time-weighted average change from baseline viral load in NP sample through day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

Note: Time-weighted average of change from baseline in viral load from day 1 to day 7 will be calculated for each patient using the trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period.

Clinical

The primary clinical endpoint is the proportion of patients who died or went on mechanical ventilation from day 6 through day 29 and from day 1 through day 29.

Phase 1/2 (Cohort 1)

Futility

The primary endpoint is death or mechanical ventilation.

Safety and Tolerability

Safety and tolerability endpoints are as follows:

- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Phase 2 (Cohort 2 and Cohort 3)

There are no primary endpoints for cohort 2 and cohort 3 in phase 2.

4.2. Secondary Endpoints

Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

Clinical

- Proportion of patients who went on mechanical ventilation by day 29
- Proportion of patients who died from day 6 to day 29 and from day 1 to day 29
- Proportion of patients who were discharged by day 29
- Proportion of patients who died or were readmitted to hospital over time

  Note: Readmission to hospital will be based on investigator report.
- Cumulative incidence of death over time (ie, overall survival)
- Cumulative incidence of mechanical ventilation over time
- Cumulative incidence of death or mechanical ventilation over time
- Time to discharge

Safety and Tolerability

- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Phase 1/2 (Cohort 1)

Clinical Efficacy

The key secondary endpoint is death or mechanical ventilation.

Other secondary endpoints include:

Virologic Efficacy

- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples

  Note: Time-weighted average of change from baseline in viral load from day 1 to day 7 will be calculated for each patient using the trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period.

- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 11, as measured by RT-qPCR in NP swab samples
- Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to each post-baseline timepoint until day 29, as measured by RT-qPCR in NP swab samples
- Change from baseline in viral load at each post-baseline timepoint through day 29, as measured by RT-qPCR in NP swab samples
- Time to sustained negative RT-qPCR (negative RT-qPCR with no subsequent) positive

Clinical Efficacy

- All-cause death
- Mechanical ventilation
- Proportion of patients who died or went on mechanical ventilation by day 29
- Proportion of patients who died by day 29
- Proportion of patients who went on mechanical ventilation by day 29
- Time to discharge

PK/ADA

- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADA and (in phase 2 and phase 3 only) NAb to REGN10933 and REGN10987

Phase 3 (Cohort 1) and Phase 2 (Cohort 1A), Separately

The secondary endpoints include:

Virologic Efficacy

Endpoint	Timepoint	Population
Time-weighted average change from baseline viral load in NP sample	Through day 7	mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 7	Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	Seronegative mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	mFAS
Time-weighted average change from baseline viral load in NP sample	Through day 11	Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS
Time-weighted average change from baseline, change from baseline, and percent change from baseline in viral load in NP sample	Through each post-baseline timepoint until day 29	1. Seronegative mFAS, 2. Baseline Viral load categories ($>10^5$, $>10^6$ copies/mL) mFAS, 3. mFAS

Clinical Efficacy

- Proportion of patients who went on mechanical ventilation by day 29 (as applicable)
- Proportion of patients who died from day 6 to day 29 and from day 1 to day 29
- Proportion of patients who were discharged by day 29
- Proportion of patients who died or were readmitted to hospital over time

  Note: Readmission to hospital will be based on investigator report.
- Cumulative incidence of death over time (ie, overall survival)
- Cumulative incidence of mechanical ventilation over time (as applicable)
- Cumulative incidence of death or mechanical ventilation over time (as applicable)
- Time to discharge

Safety and Tolerability

- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADAs and NAbs to REGN10933 and REGN10987

Phase 2 (Cohort 2 and Cohort 3)

PK/ADA

- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADAs and NAbs to REGN10933 and REGN10987

4.3. Exploratory Endpoints

The exploratory endpoints include:

- 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 (NLR) 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 (CRP) at each visit through day 29
- Change and percentage change in lactate dehydrogenase (LDH) at each visit through day 29

The exploratory long COVID endpoints for the sub-study are listed below.

- Proportion of patients with ≥1 symptom from SE-LC19 Category A by day 180
- Proportion of patients with ≥1 symptom from SE-LC19 Category B by day 180
- Proportion of patients with ≥1 symptom from SE-LC19 Category C by day 180
- Proportion of patients with ≥2 symptoms from SE-LC19 Category A by day 180
- Proportion of patients with ≥2 symptoms from SE-LC19 Category B by day 180
- Proportion of patients with ≥ 2 symptoms from SE-LC19 Category C by day 180

Note: SE-LC19 symptom categories are provided in Table 4.

- Change from baseline in viral load through day 29, and at day 120 and day 169, as measured by RT-qPCR in nasopharyngeal swab samples
- Proportion of patients with positive SARS-CoV-2 test results after randomization through day 169

Additional analyses related to psychometric validation of the SE-LC19 as well as potential biomarkers predicting long COVID will be outlined in separate SAP(s).

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description corresponding study procedures, refer to Section 9.2.3.

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, targeted medical history, and targeted medication history for each patient.

5.2. Efficacy Variables

Efficacy variables include viral load (log_{10} copies/mL), oxygen supplementation status, hospitalization and readmission status, and all-cause mortality.

5.3. Safety Variables

Safety variables include incidence of TEAEs (grade 3 or 4; for phase 1 only), treatment-emergent SAEs, and treatment-emergent AESIs (as defined in Section 10.1.3).

5.4. Pharmacokinetic Variables

For phase 1, the PK variables are the concentration of REGN10933, and REGN10987 in serum and time. For phase 2, the PK variables are the concentration of REGN10933, and REGN10987 in serum and time. The PK sampling time points are specified in the schedule of events (Table 1 for phase 1; Table 2 for phase 2 and phase 3).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, time-point/visit, and in phase 2 and phase 3 only, NAb status. Samples in this study will be collected at the clinic visits specified in the schedule of events (Table 1 for phase 1; Table 2 for phase 2 and phase 3).

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables include, but not be limited to, parameters reported in complete blood counts with differential, and levels of D-dimer, ferritin, CRP, LDH, serum cytokines, complement, cardiac biomarkers, and parameters related to long COVID questionnaires.

These results may be reported outside of the clinical study report (CSR).

6. STUDY DESIGN

6.1. Study Description and Duration

This study is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the futility or efficacy, safety, and tolerability of REGN10933+REGN10987 in hospitalized adult patients with COVID-19. The study will be conducted in approximately 100 sites, in the US and other countries.

Eligible patients who have been hospitalized for ≤72 hours at screening will be enrolled in 1 of 4 cohorts* based on disease severity at randomization (as defined in Section 6.1.3).

Phase 2 will initiate following IDMC clearance of a pooled phase 1 sentinel safety group across 2 studies (R10933-10987-COV-2066 and R10933-10987-COV-2067), and after initiation will enroll concurrently with phase 1. Once phase 2 is active, phase 1 will continue to enroll to completion, but phase 2 enrollment does not require the completion of phase 1 enrollment (for complete description and rationale for this process, refer to Section 3.2.1.1).

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

Note: On 09 April 2021, the Sponsor made a business decision to terminate patient enrollment in this study due to low recruitment rates. Patients who had been enrolled will continue to be followed up according to the Schedule of Events (Section 9.1). In addition, enrolled patients at select sites may be reconsented to protocol amendment 8 US and followed in an exploratory sub-study for an extended period to monitor for symptoms of long COVID.

6.1.1. Study Design

Phase 1 (Cohort 1 only)

Phase 1 will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in 60 patients from cohort 1.

Patients may receive background standard-of-care for COVID-19 per local guidelines, including direct and immune-based treatments (for exceptions, see Section 7.2.2).

Patients will be randomized in a 1:1:1 allocation ratio to one of the following:

- REGN10933+REGN10987 2.4 g (1.2 g of each mAb) IV single dose
- REGN10933+REGN10987 8.0 g (4.0 g of each mAb) IV single dose
- Placebo IV single dose

Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) and Phase 3 (Cohort 1)

In phase 2, the efficacy, safety, and tolerability of REGN10933+REGN10987 will be evaluated in patients who have been hospitalized for ≤72 hours at screening. Patients will be enrolled in cohort 1A, cohort 1, cohort 2*, or cohort 3*.

** Per IDMC recommendation first received on 30 October2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

Statistical analyses will be conducted separately in each cohort.

In addition to background standard-of-care, patients in each cohort will be randomized in a 1:1:1 allocation ratio to one of the following:

- REGN10933+REGN10987 2.4 g (1.2 g of each mAb) IV single dose
- REGN10933+REGN10987 8.0 g (4.0 g of each mAb) IV single dose
- Placebo IV single dose

Randomization in each cohort will be stratified as described in Section 8.6.

Note that patients in cohort 1 enrolled after the first 691 patients (including phase 1 patients) will follow the phase 2 schedule of events but will be considered enrolled under phase 3.

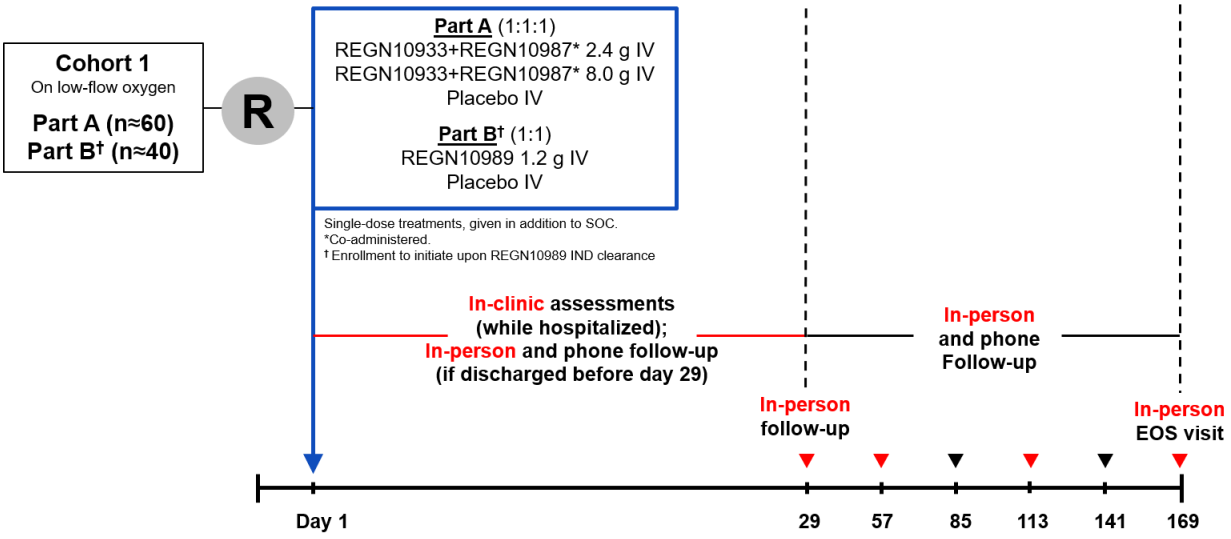
6.1.2. Study Duration

Phase 1 (Cohort 1 only)

The phase 1 portion of the study will last up to 170 days. See Table 1 for the schedule of events and sample collections:

- **Screening/Baseline**: Patients will undergo a screening and baseline period for up to 2 days (day -1 to 1).
- **Hospitalization and post-discharge period**: Patients will be assessed daily up to day 29 while hospitalized. Patients who are discharged before day 29 will be followed up —in person for sample collections, and may also be followed up by phone or telemedicine for assessments. After day 29, all patients will be followed up monthly.
- **End of study (EOS)**: On day 169, patients will have an in-person EOS visit for sample collection and assessments.

Figure 2: Study Flow Diagram, Phase 1



Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) and Phase 3 (Cohort 1)

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

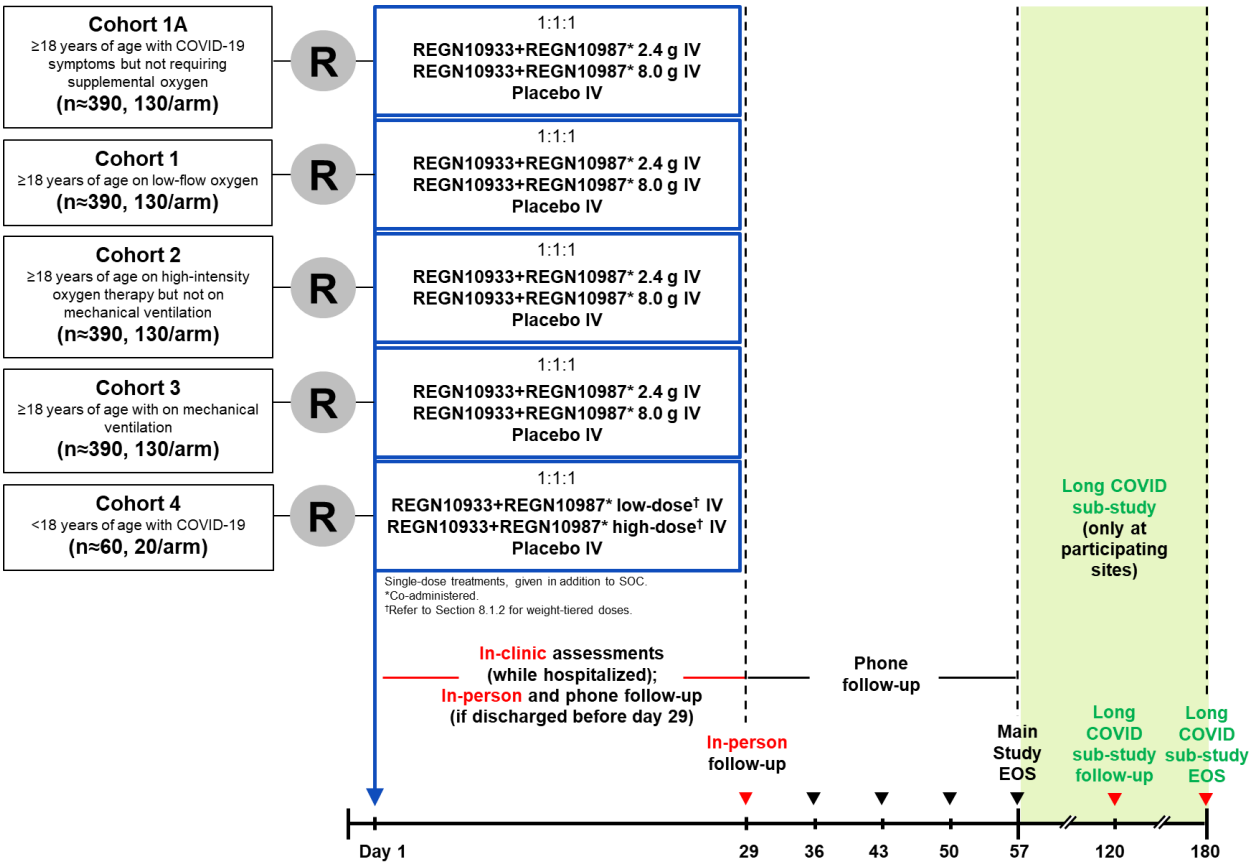
The phase 2 and phase 3 portions of the study will last up to 58 days. See Table 2 for a schedule of events and sample collections.

Patients in phase 2 (cohort 1A) and phase 3 (cohort 1) who consent to the **long COVID sub-study** at participating sites will follow the main study Schedule of Events (Table 2) until day 57, then

follow the long COVID sub-study Schedule of Events (Table 3) from day 58 to day 180. Patients who do not consent to these additional assessments will follow Table 2 until day 57.

- **Screening/Baseline**: Patients will undergo a screening and baseline period for up to 2 days (day -1 to 1).
- **Hospitalization and post-discharge period**: Patients will be assessed daily up to day 29 while hospitalized. Patients who are discharged before day 29 will be followed up in person for sample collections, and may also be followed up by phone or telemedicine for assessments. After day 29, all patients will be followed up weekly.
- **End of study (for patients <u>not</u> participating in the long COVID sub-study at participating sites)**: On day 57, patients will be followed up by phone or telemedicine for an EOS visit.
- **Long COVID sub-study follow-up (at participating sites)**: On day 120, patients will be followed up for questionnaires and sample collections.
- **Long COVID sub-study end of study (at participating sites)**: On day 180, patients will be followed up for questionnaires and sample collections.

Figure 3: Study Flow Diagram, Phase 2 and Phase 3



** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

Phase 3

In phase 3, patients will be assessed daily up to day 29 for clinical improvement. After day 29, patients will be followed-up until EOS on day 57.

6.1.3. Description of Study Cohorts

Eligible patients who have been hospitalized for ≤72 hours at screening will be enrolled in 1 of 4 cohorts* based on disease severity at randomization:

- **Cohort 1A**: With COVID-19 symptoms but not requiring supplemental oxygen
- **Cohort 1**: O_2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device
- **Cohort 2***: On high-intensity oxygen therapy† but not on mechanical ventilation

  †High-intensity oxygen therapy is defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO_2, or use of non-invasive ventilation to treat hypoxemia.
- **Cohort 3***: On mechanical ventilation

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

6.1.4. Study Stopping Rules

6.1.4.1. Individual Patient Stopping Rules

For an individual patient, the infusion rate can be slowed, interrupted, or stopped if there is a suspected drug-related event during the infusion suggestive of severe hypersensitivity or an infusion-related reaction, as per investigator discretion if it is deemed to be in the patient's best interest (see Section 8.5). As this is a single dose study, there are no other study drug discontinuation rules.

Patient stopping rules from the study include withdrawal of consent.

6.1.4.2. Study Stopping Criteria

The Sponsor may decide to stop or make adaptations to the study based upon the recommendations by an IDMC and/or review of the totality of evidence (see Section 6.2.1).

A treatment arm may be dropped if there is a clinically meaningful imbalance between treatment arms in both of the following criteria:

- Incidence of treatment-emergent SAEs evaluated as related to study treatment

  and
- A risk-benefit imbalance based upon any key efficacy and safety endpoint of the study such that one dosing arm appears to be doing substantially better than another without requiring any specific statistical level of precision

6.1.5. End of Study Definition

The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.1.6. Definition of Study Completion

For individual patients, study completion is defined as collection of vital status information on their projected EOS date. All measures will be taken to obtain vital status information on the projected EOS date, and all patients with recorded vital status information at projected EOS date will be considered study completers. The end of study is considered day 169 (for phase 1) or day 57 (for phase 2) (Section 9.1).

6.2. Study Committees

6.2.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor patient safety and efficacy data. The IDMC can make recommendations about early study closure or changes to the study conduct. The operation of the IDMC is governed by a charter describing further details, such as procedures (including but not limited to periodic safety monitoring) and requirements for reporting its observations to the Sponsor.

An IDMC will review pooled safety data up to day 3 in the sentinel safety group as described in Section 3.2.1.1. In addition, the IDMC will conduct periodic data reviews, for instance, after all patients are enrolled into phase 1. Additional periodic reviews will be conducted during phase 2 and 3 of this study as detailed in the IDMC charter. These data reviews will include all available efficacy and safety data, including deaths, from all enrolled study participants up to the data cut-point for the analysis. The IDMC will meet regularly throughout the course of the study to review safety data and make recommendations on study conduct.

6.2.2. Sponsor Review Committee

Periodic data reviews may be performed by selected unblinded senior Sponsor physicians and a statistician with no direct involvement in the study. Reviews will assess the totality of evidence and may be used to determine study adaptations (see Section 3.2.1.2).

6.3. Planned Interim Analysis

A description of the statistical methods to be employed is in Section 11.5, and blinding implications are discussed in Section 8.7.

No interim analyses are planned.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Enrolled

See Section 8.1 for treatment arms.

On 30 October 2020, an IDMC recommended pausing patient enrollment into cohort 2 and cohort 3 based on a potential safety imbalance, while proceeding with enrollment in cohorts 1A and 1. This IDMC recommendation was reiterated through 19 February 2021, and study investigators were advised by the Sponsor to follow all ongoing patients through their end of study visit as per the protocol. This IDMC recommendation on enrollment was maintained for the duration of the study.

Subsequently, on 09 April 2021, the Sponsor made a business decision to terminate patient enrollment due to low recruitment rates. This decision was not based on any safety concerns. Accordingly, phase 3 cohort 1 and phase 2 cohort 1A enrollment were prematurely terminated due to slow enrollment rate. Until this time, only cohort 1 patients were enrolled into the phase 3 portion of the study.

Overall, approximately 2252 patients were randomized in this study:

Phase 1

- **Cohort 1**: 60 patients

Phase 2

- **Cohort 1A**: 609 patients
- **Cohort 1**: 629 patients
- **Cohort 2**: 164 patients
- **Cohort 3**: 35 patients

Prematurely terminated phase 3

- **Cohort 1** (ie, patients randomized after 01 December 2020): 755 patients

7.2. Study Population

The study population will consist of hospitalized adult patients with COVID-19.

7.2.1. Inclusion Criteria

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

1. Has provided informed consent (signed by study patient or legally acceptable representative)
2. Male or female adult ≥18 years of age (or country's legal age of adulthood) at randomization
3. Has SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such

as NP, nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization and no alternative explanation for current clinical condition. A historical record of positive result from test conducted ≤72 hours prior to randomization is acceptable.

4. Has symptoms consistent with COVID-19, as determined by investigator, with onset ≤10 days before randomization
5. Hospitalized for ≤72 hours with at least 1 of the following at randomization; patients meeting more than one criterion will be categorized in the most severely affected category:
   a. **Cohort 1A:** With COVID-19 symptoms but not requiring supplemental oxygen
   b. **Cohort 1:** Maintains O_2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device

      Note: Sites located in high-altitude areas (>1500 m above sea level) should refer to Table 9 to get the appropriate high-altitude equivalents for sea-level oxygenation measurements.
   c. **Cohort 2*:** High-intensity oxygen therapy without mechanical ventilation, where high-intensity is defined as receiving supplemental oxygen delivered by 1 of the following devices:
      – Non-rebreather mask (with an SpO_2 ≤96% while receiving an oxygen flow rate of at least 10 L/min)
      – High-flow device (eg, AIRVO™ or Optiflow™) with at least 50% FiO_2
      – Non-invasive ventilator, including continuous positive airway pressure (CPAP) to treat hypoxemia (excluding isolated use for sleep-disordered breathing)
   d. **Cohort 3*:** On mechanical ventilation

   ** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*
6. **Long COVID sub-study**: Is able to understand and complete study-related questionnaires

7.2.2. Exclusion Criteria

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

1. **Phase 1 only:** Patients maintaining O_2 saturation >94% on room air

   Note: For sites in high-altitude areas, refer to Table 9. Patients on room air will not be excluded from phase 2.
2. In the opinion of the investigator, unlikely to survive for >48 hours from screening
3. Receiving extracorporeal membrane oxygenation (ECMO)
4. Has new-onset stroke or seizure disorder during hospitalization
5. Initiated on renal replacement therapy due to COVID-19
6. Has circulatory shock requiring vasopressors at randomization

Note: Patients who require vasopressors for sedation-related hypotension or reasons other than circulatory shock may be eligible in this study.

7. Patients who have received convalescent plasma, IVIG, or mAbs against SARS-CoV-2 (eg, bamlanivimab) within 5 months prior to randomization or plan to receive during the study period for any indication
8. Participation in a clinical research study, including any double-blind study, evaluating an investigational product within 30 days and less than 5 half-lives of the investigational product prior to the screening visit

   Note: The use of remdesivir, hydroxychloroquine, or other treatments (except for COVID-19 convalescent plasma or IVIG) being used for COVID-19 treatments in the context of the local standard-of-care or an open-label study or compassionate use protocol is permitted.
9. Any physical examination findings, history of illness, and/or concomitant medications that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study.
10. Known allergy or hypersensitivity to components of study drug
11. Pregnant or breastfeeding women
12. 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.

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or Sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patient who are withdrawn prematurely from the study will be asked to complete an early termination visit and have follow-up contact as described in Section 9.1.3.

7.4. Replacement of Patients

Patients prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Instructions on dose preparation are provided in the pharmacy manual. See Section 8.6 for the method of treatment allocation.

Phase 1, Phase 2, and Phase 3

- Co-administered REGN10933+REGN10987 combination therapy 2.4 g (1.2 g of REGN10933 plus 1.2 g of REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy 8.0 g (4.0 g of REGN10933 plus 4.0 g of REGN10987) IV single dose

- Placebo IV single dose

8.2. Background Treatments

Patients may receive the standard-of-care for the treatment of COVID-19 per local guidelines (if not specified in the exclusion criteria; see Section 7.2.2). Background treatments may include:

- Antiviral therapies (remdesivir or other)
- Immune-based therapies (tocilizumab, sarilumab, steroids, or other)
- Antiviral and immune-based therapies

8.3. Rescue Treatment(s)

Patients may receive rescue therapy for the treatment of COVID-19 per local standard-of-care. Rescue treatment(s) will not be provided as part of the study.

8.4. Dose Modification and Study Treatment Discontinuation Rules

This is a single dose study. Dose modification for an individual patient is not allowed. Study treatment discontinuation is not applicable to this study.

8.5. Management of Acute Reactions

8.5.1. Infusion-Related Reactions and Hypersensitivity Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use if required for treatment. All grade ≥2 infusion-related reactions and grade ≥2 hypersensitivity reactions (using the CTCAE severity scale specified in Section 10.2.4) must be reported as AESIs (see Section 10.2.3).

8.5.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following adverse events are observed:

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.5.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and **not** restarted if any of the following adverse events occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least 1 of the following:**

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.6. Method of Treatment Assignment

Patients will be randomized according to a central randomization scheme using an interactive web response system (IWRS).

Phase 1

60 patients will be randomized in a 1:1:1 allocation ratio to 1 of the following:

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

Randomization will be stratified by type of background standard-of-care being administered for COVID-19 at randomization as follows:

- Antiviral therapies (remdesivir or other)

- Non-antiviral therapies (immune-based therapies, both antiviral and immune-based therapies, or no COVID-19-specific treatment)

Phase 2

Note: Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, randomization to cohort 2 and cohort 3 has been placed on hold.

For each of the study cohorts in phase 2, patients will be randomized in a 1:1:1 ratio to receive 1 of the treatments below:

- Co-administered REGN10933+REGN10987 combination therapy 2.4 g (1.2 g of REGN10933 plus 1.2 g of REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy 8.0 g (4.0 g of REGN10933 plus 4.0 g of REGN10987) IV single dose
- Placebo IV single dose

Randomization will be stratified by country and type of background standard-of-care being administered for COVID-19 at randomization as follows:

- Antiviral therapies (remdesivir or other)
- Non-antiviral therapies (immune-based therapies, both antiviral and immune-based therapies, or no COVID-19-specific treatment)

Phase 3

Patients will be randomized in a 1:1:1 ratio to receive 1 of the treatments below:

- Co-administered REGN10933+REGN10987 combination therapy 2.4 g (1.2 g of REGN10933 plus 1.2 g of REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy 8.0 g (4.0 g of REGN10933 plus 4.0 g of REGN10987) IV single dose
- Placebo IV single dose

Randomization will be stratified by country and type of background standard-of-care being administered for COVID-19 at randomization as follows:

- Antiviral therapies (remdesivir or other)
- Non-antiviral therapies (immune-based therapies, both antiviral and immune-based therapies, or no COVID-19-specific treatment)

The treatment arms, patient cohorts, sample size, and treatment allocation scheme for phase 3 may be reconsidered after review of phase 1/2 data.

8.7. Blinding

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for IV administration. The drug infusion solution must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and patients.

Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments in all phases of the study.

Selected individuals from the Sponsor not involved in the conduct of the study may have access to unblinded phase 1 or phase 2 data as needed for safety review or other data review (see Section 6.2.2). The team performing the interim data reviews will be separate from the ongoing study team. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for this study.

Anti-drug antibody, drug concentration, and biomarker results will not be communicated to the sites, and the Sponsor's blinded operational team will not have access to results associated with patient identification until after the database is locked.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment.

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patients will be unblinded
- Unblinding is performed using the IWRS, which will notify the Sponsor. The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If the study pharmacist(s)/designee is not available, the investigator for the site will unblind the patient.
- If the IWRS is unavailable, the investigator will ask the unblinded study pharmacist(s)/designee to perform manual unblinding. All manual unblinding procedure will be adequately documented, including the reason why the IWRS was not used.
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label unblinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the patient.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed at the site with approval by the Sponsor or returned to the Sponsor or designee.

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- Dispensed to each patient
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the Sponsor or designee

All accountability records must be made available for inspection by the Sponsor and regulatory agency inspectors; photocopies must be provided to the Sponsor at the conclusion of the study.

8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the Sponsor and regulatory agency inspectors.

8.10. Concomitant Medications

Any treatment administered from–the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

If the local standard-of-care per written policies or guidelines include remdesivir or other agents, then they are permitted during the study (if not specified in the exclusion criteria; see Section 7.2.2).

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications (listed in Section 9.2.3.3) will be captured in this trial. The select list of medications will be assessed according to the schedule of events (Table 1 for phase 1; Table 2 for phase 2 and phase 3).

8.10.1. Prohibited and Permitted Medications

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment (Section 7.2.2).

Patients may otherwise continue their normal regimen of medications and procedures.

SARS-CoV-2 Vaccination. Current CDC guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody treatment (eg, REGN10933+REGN10987) (CDC, 2020):

> *Based on the estimated half-life of such therapies as well as evidence suggesting that reinfection is uncommon in the 90 days after initial infection, vaccination should be deferred for at least 90 days, as a precautionary measure until additional information becomes available, to avoid interference of the antibody treatment with vaccine-induced immune responses.*

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit for phase 1 (Table 1) and phase 2 (Table 2).

9.1.1. Phase 1 (Cohort 1 only)

Table 1: Schedule of Events for Phase 1

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																						EOS
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	57	85	113	141	169
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	9	13	17	21	25
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33	34
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±7	±7	±7	±7	±7
Screening/Baseline Only																											
Informed consent	X																										
PGx sub-study consent (optional)[3]	X																										
Inclusion/exclusion	X																										
Antigen or molecular diagnostic test for SARS-CoV-2 (local)[4]	X																										
Demographics	X																										
Medical history[5]	X																										
Weight and height	X																										
Randomization		X																									
Treatment																											
Study drug administration			X																								
Safety Assessments																											
Vital signs[6]	X	X	X																								
Treatment-emergent grade ≥2 infusion-related reactions[7,8]			← Continuous monitoring →																								
Treatment-emergent grade ≥2 hypersensitivity reactions[7,8]			← Continuous monitoring →																								
Treatment-emergent SAEs[7,8]			← Continuous monitoring →																								
Grade 3 or 4 TEAEs[7,8]			← Continuous monitoring →																								
Targeted concomitant medications[8,9]	X	X	← Continuous monitoring →																								
Post-discharge phone follow-up[8]												X							X		X		X	X	X	X	X	X
Pregnancy test (WOCBP)[10]	X																											X
Local Laboratory Testing																											

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																					EOS
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	57	85	113	141	169
	Screen	Pre-Dose	Dose	Post-Dose																						
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	9	13	17	21	25
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33	34
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±7	±7	±7	±7	±7
Hematology (including differential)[11]	X				X						X												X	X				
Blood chemistry (including AST, ALT, CRP, ferritin, LDH)[11]	X				X						X												X	X				
Coagulation tests (D-dimer, PT/INR, aPTT)[11]	X				X						X												X	X				
Efficacy Assessments (Virologic)																												
Saliva for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X					
Nasal swab for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X					
NP swab for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X					
Efficacy Assessments (Clinical/Oxygen Status)																												
Oxygen delivery device status[12]		X[12]	X[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Vital status[12]		X[12]	X[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Hospitalization status[12]		X[12]	X[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Pharmacokinetics/Immunogenicity																												
Serum for PK[13]		X[14]		X[14]	X		X		X		X								X				X	X		X		X
Serum for ADA[15]		X[15]			X																		X	X				X
Pharmacodynamic/Biomarkers																												
Serum for serology		X																					X					X
Pharmacogenomics Sub-Study (Optional)																												
Blood for RNA[3]		X[3]																										
Blood for DNA[3]		X[3]																										

9.1.1.1. Footnotes for Table 1 Schedule of Events (Phase 1)

1. Every effort should be made to perform all screening and baseline activities on the same day. Randomization within the Interactive Response Technology (IRT) system and administration of study drug should occur on the same day (day 1). All samples will be collected before study drug administration at the baseline visit except post-infusion PK samples.
2. For a given day, the visit may occur in clinic, as a home-based visit (defined as visits by home health care staff, at mobile units, and/or testing centers), or by phone. All samples will be collected as indicated whether the patient is hospitalized or has been discharged.
3. Patients must provide separate consent to collect blood samples as part of the optional pharmacogenomics (PGx) sub-study. Blood sample for RNA must be collected pre-dose on day 1. Blood sample for DNA should be collected at the screening/baseline visit but may be collected at any visit.
4. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
5. Medical history should include collecting onset of pneumonia symptoms.
6. Vital signs (including respiratory rate, temperature, blood pressure, heart rate, and SpO_2) will be taken as described in Section 9.2.3.1.

   For patients in the phase 1 sentinel safety group only (Section 3.2.1.1), vital signs will be taken once before the infusion, every 15 minutes during the infusion, every 30 minutes for the first 2 hours after the infusion is completed, and then once per hour for the following 4 hours. **For all other patients**, vital signs will be taken once before the infusion and once after the infusion is completed.
7. Only TEAEs (grade 3 or 4), treatment-emergent SAEs, and treatment-emergent AESIs will be recorded in the eCRF.
8. Patients discharged from the hospital may receive phone follow-up for TEAEs (grade 3 or 4), treatment-emergent SAEs, treatment-emergent AESIs, and/or targeted concomitant medications as indicated in Table 1 (post-discharge phone follow-up). These visits may occur in addition to any in-person visit listed for the given day. Phone visits will have a window of ±1 day.
9. Medications will be reviewed and recorded. Only the targeted medications listed in Section 9.2.3.3 will be recorded in the eCRF.
10. Pregnancy testing will be performed locally in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.3.4 for more information on pregnancy testing and contraceptive measures.
11. Hematology, blood chemistry, and coagulation tests will be collected at the visits indicated and results will be entered in the eCRF. Hematology, blood chemistry, and coagulation tests must be collected prior to randomization. Testing will be performed locally, and standard-of-care labs are acceptable.

12. Clinical and oxygen status will be collected 3 times during the screening/baseline visit period: prior to randomization, just prior to dosing, and post-dose. Clinical and oxygen status will be collected and recorded in the eCRF as described in Section 9.2.5.2.
13. Actual dosing time and PK sample collection times will be recorded.
14. At the baseline visit, blood samples for PK assessment will be taken predose and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.
15. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.

9.1.2. Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*) and Phase 3 (Cohort 1)

Patients in cohort 1 enrolled after 691 patients in the cohort (including phase 1 patients) will follow the below schedule but will be considered enrolled in phase 3.

Patients who are **not** enrolled in the long COVID sub-study (at participating sites) will follow Table 2 through EOS on day 57. Patients who enroll in the long COVID sub-study will follow Table 2 from screening to day 57, and Table 3 from day 58 to EOS on day 180.

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold. All currently enrolled patients will have assessments and procedures performed according to the Schedule of Events in the protocol version to which they were last consented.*

Table 2: Schedule of Events for Phase 2 and Phase 3

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																			Follow-up Period			EOS[16]
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	36	43	50	57
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	6	7	8	9
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±3	±3	±3	±3
Screening/Baseline Only																											
Informed consent	X																										
PGx sub-study consent (optional)[3]	X																										
Inclusion/exclusion	X																										
Antigen or molecular diagnostic test for SARS-CoV-2 (local)[4]	X																										
Pregnancy test (WOCBP)[5]	X																										
Demographics	X																										
Medical history[6]	X																										
Weight and height	X																										
Randomization		X																									
Treatment																											
Study drug administration			X																								
Efficacy Assessments (Virologic)																											
NP swab for SARS-CoV-2 RT-qPCR		X			X		X		X		X		X		X		X		X		X		X				
Efficacy Assessments (Clinical/Oxygen Status)																											
Oxygen delivery device status[7]		X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital status[7]		X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hospitalization status[7]		X[7]	X[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Safety Assessments																											
Vital signs[8]		X		X																							
Treatment-emergent grade ≥2 infusion-related reactions[9,10]			← Continuous monitoring →																								
Treatment-emergent grade ≥2 hypersensitivity reactions[9,10]			← Continuous monitoring →																								
Treatment-emergent SAEs[9,10]			← Continuous monitoring →																								
Targeted concomitant medications[10,11]	X	X	← Continuous monitoring →																								

Day	Screening/Baseline[1]				Hospitalization/Post-Discharge Period[2]																			Follow-up Period			EOS[16]
	-1 to 1				Discharge Before Day 29	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16, 17, 18, 19, 20, 21	22	23, 24, 25, 26, 27, 28	29	36	43	50	57
	Screen	Pre-Dose	Dose	Post-Dose																							
Week Number	1					1	1	1	1	1	1	2	2	2	2	2	2	2	3	3	4	4	5	6	7	8	9
Visit Number	1					2	3	4	5	6	7	8	9	10	11	12	13	14	15	16-21	22	23-28	29	30	31	32	33
Window (Days)					±1								±1		±1		±1		±1		±3		±3	±3	±3	±3	±3
Post-discharge phone follow-up[10]												X							X		X		X	X	X	X	X
Pregnancy follow-up																											X
Local Laboratory Testing																											
Hematology (including differential)[12]	X				X						X								X				X				
Blood chemistry (including AST, ALT, CRP, ferritin, LDH)[12]	X				X						X								X				X				
Coagulation tests (D-dimer, PT/INR, aPTT)[12]	X				X						X								X				X				
Pharmacokinetics/Immunogenicity																											
Serum for PK[13]		X[14]		X[14]	X														X				X				
Serum for ADA[15]		X[15]			X																		X				
Pharmacodynamic/Biomarkers																											
Serum for serology		X			X																		X				
Serum for cytokines and CK-MB		X			X						X								X				X				
Serum for research and cardiac biomarkers		X			X						X								X				X				
Plasma for research and cardiac biomarkers		X			X						X								X				X				
Plasma for hsTroponin-T		X			X						X								X				X				
Pharmacogenomics Sub-Study (Optional)																											
Blood for RNA[3]		X[3]																									
Blood for DNA[3]		X[3]																									

Table 3: Schedule of Events for the Long COVID Sub-Study at Participating Sites

Day	**Long COVID Follow Up[16]**	**EOS[16]**
	120	**180**
Visit Number	**34**	**35**
Window (Days)	**±7**	**±7**
Questionnaires		
SE-LC19[17]	X	X
PGIS[17]	X	X
Return to usual health[17]	X	X
Return to usual activities[17]	X	X
SF-36[17]	X	X
WPAI+CIQ[17]	X	X
EQ-5D-5L[17]	X	X
Safety		
Treatment-emergent SAEs[9]	← Continuous monitoring →	
Hematology (including differential)[12,17]	X	X
Blood chemistry[12,17]	X	X
SARS-CoV-2 vaccination status	X	X
Sample Collections		
NP swab for SARS-CoV-2 RT-qPCR[17]	X	X
Blood for PBMCs[17]	X	X
Serum for exploratory long COVID research (SARS-CoV-2 serology, proteomics, and other research)[17]	X	X
Plasma for exploratory long COVID research[17]	X	X
Additional Adverse Events of Special Interest		
Details of positive SARS-CoV-2 local test result[18]	continuous monitoring →	
New medical diagnoses or conditions[19]	X	X
Pharmacogenomics Sub-Study (Optional)		
Blood for DNA[3]	X[3]	

9.1.2.1. Footnotes for Table 2 and Table 3 Schedule of Events (Phase 2 and Phase 3)

1. Every effort should be made to perform all screening and baseline activities on the same day. Randomization within the IRT system and administration of study drug should occur on the same day (day 1). All samples will be collected before study drug administration at baseline visit except post-infusion PK samples.
2. For a given day, the visit may occur in clinic, as a home-based visit (defined as visits by home health care staff, at mobile units, and/or testing centers), or by phone. All samples will be collected as indicated whether the patient is hospitalized or has been discharged.
3. Patients who consent to the optional pharmacogenomics (PGx) sub-study should have a blood sample for DNA collected. This may be done during any in-person study visit. Efforts should be made to consent patients to the PGx sub-study if they have not already consented. Patients who already consented to the sub-study will not be consented a second time, and patients who have already provided a DNA sample for the PGx sub-study should not have a second sample collected. Refer to Section 9.2.9.4 for more information about the PGx sub-study.
4. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
5. Pregnancy testing will be performed locally in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.3.4 for more information on pregnancy testing and contraceptive measures.
6. Medical history should include collecting onset of pneumonia symptoms.
7. Clinical and oxygen status will be collected 3 times during the screening/baseline visit period: prior to randomization, just prior to dosing, and post-dose. Clinical and oxygen status will be collected and recorded in the eCRF as described in Section 9.2.5.2.
8. Vital signs (including temperature, blood pressure, heart rate, and SpO_2) will be collected pre-dose and post-dose, as described in Section 9.2.3.1.
9. Only treatment-emergent SAEs and AESIs will be recorded in the eCRF.
10. Patients discharged from the hospital will have weekly follow-up for treatment-emergent SAEs, treatment-emergent AESIs, and/or targeted concomitant medications as indicated in Table 2 (post-discharge phone follow-up), which may occur as a phone call or an in-person visit. These visits may occur in addition to any in-person visit for sample collection listed for the given day. Phone visits will have a window of ±1 day.
11. Medications will be reviewed and recorded. Only the targeted medications listed in Section 9.2.3.3 will be recorded in the eCRF.
12. Hematology, blood chemistry, and coagulation tests will be collected at the visits indicated and results will be entered in the eCRF. Note that coagulation tests will **not** be collected as part of the long COVID sub-study. Hematology, blood chemistry, and coagulation tests must be collected prior to dosing. Testing will be performed locally, and standard-of-care labs are acceptable.
13. Actual dosing time and PK sample collection times will be recorded.

14. At the baseline visit, blood samples for PK assessment will be taken predose and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.
15. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
16. For patients who are not enrolled in the long COVID sub-study, day 57 will be the EOS per Table 2. Patients enrolled in the long COVID sub-study will follow Table 2 from screening to day 57, and Table 3 from day 58 to their EOS on day 180.

    For patients who consent to the long COVID sub-study after day 120, the day 120 sample collections may be performed outside of the specified visit window. Efforts should be made to collect these samples for all consenting patients.
17. On visit days when other assessments or sample collections are required, the site will verify that questionnaires have been completed prior to all other assessments or collections. The order of questionnaire completion is as follows: SE-LC19, PGIS, return to usual health, return to usual activities, SF-36, WPAI+CIQ, EQ-5D-5L.

    Note that questionnaires will only be administered to sites when regionally available, and will only be administered to patients who are able to complete the questionnaires in the language available at their site.

    Refer to Section 9.2.9 for additional information regarding assessments and procedures related to long COVID analyses. Note that in addition to the analyses planned in this study, exit interviews may be conducted by a third party as part of a separate study. Refer to Section 9.2.10; additional information, including study visits and windows for these interviews, will be detailed in the separate study.
18. Patients in the long COVID sub-study will be asked to report any positive SARS-CoV-2 local test results obtained during the period indicated, starting from the day at which they consent to the sub-study. Refer to Section 9.2.9.3 for additional information regarding collection and reporting.
19. For patients in the long COVID sub-study, any new medical condition(s) diagnosed after randomization will be recorded. Refer to Section 9.2.9.4 for additional information regarding collection and reporting.

9.1.3. Early Termination from the Study

Patients who are withdrawn from the study prior to day 29 will be asked to complete an early termination (ET) visit consisting of day 29 assessments and sample collections. In phase 1, patients withdrawn from the study after day 29 will be asked to complete an ET visit consisting of the EOS visit (day 169) assessments and sample collections. In phase 2, patients withdrawn from the study after day 29 will be asked to complete an ET phone visit consisting of the EOS visit (day 57) assessments.

All patients who are withdrawn from the study will be contacted by phone to obtain vital status. For patients in phase 1, this call will occur on day 169. For patients in phase 2, this will occur on day 57.

9.1.4. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of treatment-emergent SAEs, AESIs, and (for phase 1) grade 3 or 4 TEAEs, or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the schedule of events in Section 9.1.

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

9.2.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2. Optional informed consent may be obtained for participation in the pharmacogenomic sub-study described in Section 9.2.10.

9.2.1.2. Diagnostic Test for SARS-CoV-2

The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2, either at screening or by historical record (refer to Section 7.2.1 for detailed screening requirements). For tests performed at screening, the local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF. If testing was performed outside of the allowed window (Section 7.2.1), a new test is required for study inclusion.

9.2.1.3. Demographics

See Section 5.1.

9.2.1.4. Medical History

Medical history will include the following:

- Onset of pneumonia symptoms (collected on the Pneumonia Status at Baseline eCRF)
- Prior and current symptoms related to COVID-19
- Menopausal history

9.2.1.5. Weight and Height

Weight and height will be recorded at the screening/baseline visit.

9.2.2. Treatment

See Section 8.1.

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs will include respiratory rate (phase 1 only), temperature, blood pressure, heart rate, and SpO_2. Vital signs will be assessed according to the schedule of events in Section 9.1.

9.2.3.1.1. Respiratory Rate (Phase 1 Only)

In phase 1, respiratory rate (per minute) will be measured before and after infusion.

9.2.3.1.2. Body Temperature

Body temperature measurement will occur before taking antipyretics or more than 4 hours after last dose of antipyretics. Temperature will be measured to monitor the patient's status regarding fever. Temperature may be measured using the following methods: axilla, oral, tympanic, or temporal according to local hospital protocols and according to the manufacturer's instructions for use of the device. Body temperature should be measured using the same method each time. Temperature should be measured after at least 5 minutes of rest (supine or sitting).

9.2.3.1.3. Blood Pressure

Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position.

9.2.3.1.4. Heart Rate

Pulse (per minute) will be measured.

9.2.3.1.5. Oxygen Saturation Level (SpO_2) and Fraction of Inspired Oxygen (FiO_2)

Supplemental oxygen/FiO_2 use will be measured to monitor the patient's status regarding gas exchange. As applicable, the following will be recorded:

- Oxygen flow rate in L/min (if not mechanically ventilated)
- FiO_2 (if mechanically ventilated)
- Resting SpO_2 (in %) will be measured in all patients to assess arterial oxyhemoglobin saturation. SpO_2 will be measured using a fingertip or similar non-invasive device following 5 minutes of rest (inactivity) while supine, semi-recumbent, or sitting and will only be measured in the presence of a good SpO_2 wave form. SpO_2 must be measured simultaneously with recorded supplemental oxygen/FiO_2 data.

9.2.3.2. Adverse Event Monitoring

Treatment-emergent serious adverse events (as defined in Section 10.2.1) and treatment-emergent AESIs (as defined in Section 10.2.3) will be recorded. In phase 1, TEAEs (grade 3 or 4) will also be recorded.

9.2.3.3. Targeted Medication and Procedures Review

A targeted list of the following concomitant medications and procedures will be recorded in the eCRF:

- Putative COVID-19 treatments (eg, remdesivir, convalescent serum, IVIG, IL-6 receptor inhibitors [eg, sarilumab, tocilizumab], JAK inhibitors [eg, baricitinib], ivermectin)
- SARS-CoV-2 vaccinations
- Antipyretics (eg, aspirin, acetaminophen, ibuprofen)
- Anticoagulants (eg, enoxaparin, warfarin, rivaroxaban)
- Immunosuppressants (eg, cyclosporine A, corticosteroids)
- Interferon beta
- Theophylline
- Antiepileptics (eg, carbamazepine, divalproex, phenytoin)
- Antiarrhythmics (eg, digoxin, disopyramide, procainamide)
- Antivirals, antibacterial, and antifungals
- Antiparasitics (chloroquine or hydroxychloroquine)
- Angiotensin receptor blockers (eg, losartan, valsartan)
- Angiotensin converting enzyme inhibitors (eg, benazepril, lisinopril)
- Treatment related to reported AEs (eg, supplemental oxygen, packed red blood cells)

9.2.3.4. Pregnancy Test and Reporting for Women of Childbearing Potential

Pregnancy testing may be satisfied by either serum pregnancy test or by urine β-HCG. Pregnancy tests are a requirement for WOCBP only. Pregnancy test will be performed at the local laboratory.

WOCBP and female partners of male patients will be advised to use highly-effective contraception for 6 months after the receiving study drug (see Section 7.2.2).

In phase 2, WOCBP will be followed up for any pregnancy at the EOS phone visit.

9.2.4. Laboratory Testing

Blood Chemistry

Samples for laboratory testing will be collected at visits according to the schedule of events in Section 9.1.

Tests will include:

Sodium	Blood urea nitrogen (BUN)	Alkaline phosphatase
Potassium	Aspartate aminotransferase (AST)	Creatinine
Chloride	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Carbon dioxide	Total bilirubin	Lactate dehydrogenase (LDH)
Glucose	Albumin	C-reactive protein (CRP)
Ferritin		

Hematology

Hematology samples will be analyzed by a local laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

The results of hematology testing that is performed as part of the patient's standard-of-care will be shared with the Sponsor. When CBC is performed as part of the patient's clinical care, the results will be entered in eCRF according to the schedule of events in Section 9.1.

Tests will include:

Hemoglobin	*Differential:*	Neutrophils
Hematocrit		Lymphocytes
Red blood cells (RBCs)		Monocytes
White blood cells (WBCs)		Basophils
Platelet count		Eosinophils

Other Laboratory Tests

Coagulation tests: D-dimer, prothrombin time (PT/INR), activated partial thromboplastin time (aPTT)

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as treatment-emergent SAEs are provided in Section 10.1.1.

9.2.5. Efficacy Procedures

9.2.5.1. Sample Collection for RT-qPCR Analysis

Virologic samples will be used to determine presence or absence of SARS-CoV-2 virus, including at baseline, and to measure viral load via RT-qPCR analysis. Samples may additionally be used for exploratory viral RNA sequencing (NP, nasal, saliva) and/or viral culture (NP, nasal). Only NP swabs will be collected for virology testing after phase 1. NP samples with an original RT-qPCR result above the Upper Limit of Quantification (ULOQ) will be diluted and retested by RT-qPCR. Additional details regarding sample collection and analysis can be found in the laboratory manual.

Patient refusal to provide virologic samples will not be noted as a protocol deviation.

9.2.5.2. Clinical and Oxygen Status

Clinical and oxygen status will be collected and recorded in the eCRF as follows:

- **Oxygen delivery device status:** day 2: record the worst status since 2 hours after EOI up to 00:00 on day 2; day 3 and later: record the worst status in the past 24 hours (00:00 to 00:00) of that study day (eg, for day 3, record the worst status between 00:00 and 23:59 on day 3).
- **Vital Status:** Record vital status (dead or alive) of the day and record any death (if applicable) on the day of death.
- **Hospitalization Status:** Starting on day 2, record daily whether patient is hospitalized without requiring medical care or discharged.

These records will be used to calculate the daily ordinal scale (Section 9.2.5.2.4).

9.2.5.2.1. Oxygen Delivery Device Status

The type of oxygen delivery device used will be recorded (eg, nasal cannula, simple face mask, non-rebreather mask, non-invasive ventilation, or invasive mechanical ventilation).

The most invasive type of oxygen devices used in the past 24 hours (00:00 to 00:00) will be recorded.

9.2.5.2.2. Vital Status

The patients' vital status (ie, whether they are alive or not) as of the current day will be recorded.

9.2.5.2.3. Hospitalization Status

The patients' hospitalization status (ie, whether the patient is hospitalized requiring medical care or not and if the patient was discharged) will be recorded. This will be used to calculate the daily ordinal score.

9.2.5.2.4. Clinical Status Assessment (7-Point Ordinal Scale)

Based on the clinical and oxygen status (described in Section 9.2.5.2), an ordinal scale score will be generated automatically and used to assess clinical improvement. The ordinal scale score rates a patient's clinical status as follows (Peterson, 2017):

[1] Death

[2] Hospitalized, requiring invasive mechanical ventilation or ECMO

[3] Hospitalized, requiring non-invasive ventilation or high flow oxygen devices

[4] Hospitalized, requiring supplemental oxygen

[5] Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19-related or otherwise)

[6] Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care

[7] Not hospitalized

9.2.6. Drug Concentration and Measurements

Samples for PK assessment will be collected at the indicated timepoints in the schedule of events. For information concerning unused samples and exploratory research, refer to Section 9.2.8.

9.2.7. Immunogenicity Measurements and Samples

Samples for ADA and NAb assessments will be collected at the timepoints listed in the schedule of events. For information concerning unused samples and exploratory research, refer to Section 9.2.8.

9.2.8. Exploratory Pharmacodynamic/Biomarker Procedures

This section describes planned exploratory analyses, some of which may not be reported in the CSR.

Note that any biological samples collected during the study which are not used for their planned purpose, or for which material remains after their planned analysis, may be kept for up 15 years after study completion (or for a shorter time period if required per regional laws and regulations) for use in exploratory research related to how the study drugs work and to study SARS-CoV-2.

9.2.8.1. Virology

Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants, as well as to monitor for possible viral resistance, viral genome sequencing will be performed on all viral nucleic acid isolated from NP, nasal swab, and/or saliva samples, at baseline and in cases of a positive RT-qPCR result. Sequencing analyses will consist of the entire viral genome, including the full gene sequence that encodes the SARS-CoV-2 S protein.

Viral sequencing may be performed on post-treatment samples to assess the emergence of sequence variants and to understand the potential relationship between genetic mutations and mAb functional activity. Viral sequencing may also be done on placebo controls to determine whether

any genetic mutations observed in the mAb treatment group are naturally emergent genetic variants.

Viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.

The results of the viral sequencing may not be included in the CSR.

Viral Infectivity

To explore the effects of REGN10933+REGN10987 on infectivity of SARS-CoV-2, we may use plaque forming unit (PFU), viral culture, or subgenomic mRNA viral RT-qPCR assays. In vitro SARS-CoV-2 infectivity of cultured cells may be explored using NP samples. Infectivity of cells grown in culture may be assessed by PFU assays and/or immunofluorescence assays. We may also use sub-genomic viral mRNA transcript assays, such as RT-qPCR or subgenomic mRNA sequencing, or other measures of in vivo infectivity potential. Viral sub-genomic mRNA is transcribed only in infected cells and is not packaged into virions, and therefore an indicator of actively-infected cells. These data may be associated with other RT-qPCR measuring viral load.

9.2.8.2. Hematology for Complete Blood Count and Differential

Neutrophil-lymphocyte ratio (NLR) will be assessed, as well as other hematological biomarkers. NLR is an inflammatory marker that may serve as an independent risk factor for in-hospital mortality of patients with COVID-19. Assessment of NLR trends may therefore aid in identifying patients with COVID-19 who are at higher risk of complications (Liu, 2020) (Qin, 2020). Relationships will be evaluated between NLR and clinical outcomes in treatment versus placebo arms.

9.2.8.3. Serum and Plasma for Disease Biomarkers

Changes in concentrations of serum/plasma biomarkers associated with inflammation and disease progression will be assessed, including the relationship between concentration changes and clinical outcomes in treatment versus placebo arms. The association between changes in disease related biomarkers with clinical endpoints will be evaluated.

Biomarkers may include (but are not limited to) CRP, LDH, D-Dimer, and ferritin will be assessed as exploratory endpoints. CRP is a general inflammation marker that correlates with severity of COVID-19 including lung lesions, supplemental O_2 requirements, and death (Qin, 2020) (Young, 2020) (Wang, 2020a) (Ruan, 2020) (Luo, 2020). LDH was identified as a predictive factor for early recognition of lung injury and advanced COVID-19 cases (Han, 2020). Ferritin is a general inflammation marker associated with severity of COVID-19 (Qin, 2020). D-dimer levels >1 µg/mL have been reported to identify patients with poor prognosis for COVID-19 (Zhou, 2020).

9.2.8.4. Serological Immunoassays for Anti-SARS-CoV-2 Antibodies

To explore the impact of baseline humoral activity against SARS-CoV-2 on the response to REGN10933+REGN10987, serological immunoassays will be used to detect antibodies at baseline against the SARS-CoV-2 S protein and/or N protein. Neutralization assays may also be used to evaluate the function of endogenous baseline anti--SARS-CoV-2 antibodies. Associations will be evaluated with clinical outcomes. Measurement of antibodies against the N protein post-

treatment will also be used to evaluate whether or not REGN10933+REGN10987 effects the endogenous humoral immune response to SARS-CoV-2.

9.2.8.5. Serum and Plasma for Research

Research serum and plasma are being collected and banked for exploratory research related to COVID-19, SARS-CoV-2, REGN10933+REGN10987, host and viral biological pathways, and other mechanisms related to disease activity and clinical outcomes.

9.2.8.6. Complement

Complement activation has been hypothesized to contribute to the maladaptive inflammatory response seen in some patients with advanced COVID-19. Circulating complement biomarker concentrations may be assessed in order to understand the involvement of the classical lectin and/or alternative complement pathways in the pathogenesis of COVID-19 and clinical outcomes.

9.2.8.7. Cytokines

The initial inflammatory responses to an infection are rapid and non-specific, regulated by proinflammatory cytokines such as interleukin-6 (IL-6). As IL-6 has been implicated in the severity of COVID-19, IL-6 and other cytokines, including but not limited to, IL-8, IL-1ß, IFNγ, TNFα, IL-10 and MIP-1β may be measured. Additional cytokines may be interrogated through the use of cytokine panels.

9.2.8.8. Serum and Plasma for Cardiac Biomarkers

SARS-CoV-2 has been shown to infect the myocardium, and emerging evidence suggests that myocardial damage may be a long-term clinical consequence of COVID-19 (Lindner, 2020) (Puntmann, 2020). Cardiac biomarkers, including troponins, N-terminal pro B-type natriuretic peptide (NT-proBNP), and creatine kinase-MB (CK-MB), can be elevated in patients with COVID-19 and have been shown to correlate with adverse outcomes (Puntmann, 2020) (Sandoval, 2020) (Shi, 2020). Relationships may be evaluated between these biomarkers, as well as other biomarkers and clinical outcomes in treatment versus placebo arms.

If initial analyses reveal no signal of cardiac injury, subsequent analyses may be omitted.

9.2.9. Long COVID Sub-Study (at Participating Sites)

To better understand the nature of long COVID, as well as the potential relationship between prior treatment of SARS-CoV-2 infection with REGN10933+REGN10987 and subsequent development of long COVID, study participants in this sub-study will be evaluated using questionnaires (SE-LC19, PGIS, PGIC return to usual health, return to usual activities, SF-36, WPAI+CIQ, EQ-5D-5L), as well as NP swab and blood sample collections. All questionnaires will be administered by interviewers by phone or in person.

Note that patient-reported outcome data are generally not reportable as individual AEs, with exceptions as described in Section 10.1.1.

In addition to the procedures outlined in this study, separate exit interviews may be conducted by a third party as part of a separate study investigating the symptom experience and impact experience of COVID-19. Sites will facilitate the identification of eligible patients according to

the pre-specified eligibility criteria of the separate study, and will provide patient contact information to the third party. Patients who meet eligibility criteria for this separate study may be contacted by the third party to determine their interest in the study.

9.2.9.1. Patient-Reported Evaluation of Long COVID

Symptom Evolution of Long COVID-19 (SE-LC19)

In an effort to better understand the symptomatic course of long COVID, the Sponsor developed the Symptom Evolution of COVID-19 (SE-LC19). The SE-LC19 expands upon the SE-C19, which was developed with the aim of evaluating the acute phase of the disease course.

The SE-LC19 consists of 40 symptoms, identified based on an evaluation of the currently-available literature on symptoms associated with long COVID (CDC, 2021) (NHS, 2021) (WHO, 2021). Table 4 lists the symptoms evaluated in the SE-LC19.

Table 4: Symptoms Evaluated in the Symptom Evolution of Long COVID-19 (SE-LC19) Instrument

Symptom Evolution of Long COVID-19 (SE-LC19)			
All SE-LC19 Symptoms	**SE-LC19 Category A**	**SE-LC19 Category B**	**SE-LC19 Category C**
Altered or loss of smell	Altered or loss of smell	Altered or loss of smell	Altered or loss of smell
Altered or loss of taste	Altered or loss of taste	Altered or loss of taste	Altered or loss of taste
Body aches such as muscle pain or joint pain	Body aches such as muscle pain or joint pain	Body aches such as muscle pain or joint pain	Body aches such as muscle pain or joint pain
Cough	Cough	Cough	Cough
Fatigue	Fatigue	Fatigue	Fatigue
Headache	Headache	Headache	Headache
Shortness of breath or difficulty breathing	Shortness of breath or difficulty breathing	Shortness of breath or difficulty breathing	Shortness of breath or difficulty breathing
Chest pain		Chest pain	Chest pain
Feeling depressed	**Symptoms Included: 7**	Feeling depressed	Feeling depressed
Rapid, strong or irregular heartbeat		Rapid, strong or irregular heartbeat	Rapid, strong or irregular heartbeat
Brain fog			Brain fog
Diarrhea		**Symptoms Included: 10**	Diarrhea
Dizziness			Dizziness
Feeling Anxious			Feeling Anxious
Fever			Fever
Loss of concentration			Loss of concentration
Memory problems			Memory problems
Pins and needles or numbness			Pins and needles or numbness
Pressure or tightness in chest			Pressure or tightness in chest
Rash			Rash
Sore throat			Sore throat
Stomachache			Stomachache
Chills			
Confusion			**Symptoms Included: 22**
Difficulty sleeping			
Earache			
Feeling irritable			
Feeling lightheaded			
Hair loss			
Hot flushes			
Inability to find the right words			
Loss of appetite			
Nausea			
Phlegm			
Red or watery eyes			
Ringing or buzzing in ears			
Runny nose			
Sneezing			
Sweats			
Vomiting			
Symptoms Included: 40			

Category A: Symptoms defined as “lingering” and identified across all three guidelines.
Category B: identified across all three guidelines.
Category C: identified across at least two or three guidelines.
Guidelines: (CDC, 2021) (NHS, 2021) (WHO, 2021)

Global Impression Items

The Patient Global Impression of Severity (PGIS) questionnaire will assess the overall subjective experience of COVID-19 symptom severity over time. The Return to Usual Health and Return to Usual Activities questionnaires will evaluate whether patients have returned to their usual health or activities prior to their COVID-19 illness.

SF-36

The SF-36 is a short-form, 36-question survey assessing health and quality of life. Questions are aggregated into eight scales, which each measure a distinct aspect of health. A score from 0 to 100 is generated for each scale, where higher scores represent less disability on the scale. The scales are further aggregated into two summary scores (also ranging from 0 to 100), which measure overall physical health and mental health.

WPAI+CIQ

The Work Productivity and Activity Impairment and Classroom Impairment Questions (WPAI+CIQ) questionnaire measures the effect of a specific health problem (eg, infection with SARS-CoV-2) on work productivity and activity impairment. The specific outcomes measured by the questionnaire are absenteeism (work time missed), presenteeism (impairment while working), overall work impairment (absenteeism plus presenteeism), and activity impairment (impairment in regular activities). Each score is represented as a percentage, with higher scores indicating less productivity or greater impairment.

EQ-5D-5L

The EQ-5D-5L covers 5 health domains: mobility, self-care, usual activities, pain, and anxiety. Patients rate each domain on 5 level severity scale: having no problems, having slight problems, having moderate problems, having severe problems, and being unable to do/having extreme problems. In addition to the 5 domains, patients record their overall health on a visual analog scale, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

9.2.9.2. Nasopharyngeal Swab Sample and Blood Sample Collections (Long COVID Assessment)

Nasopharyngeal (NP) swab samples will be collected to assess the presence or absence of SARS-CoV-2 by RT-qPCR, and may be used for viral sequencing as described in Section 9.2.8.1 Additional details regarding sample collection can be found in the laboratory manual.

Serum, plasma, and PBMC samples will be collected and banked for subsequent analyses. Such analyses may include, but are not limited to, multiplex proteomic profiling, high-throughput RNA sequencing, flow cytometry, and serologic immunoassays to detect antibodies against SARS-CoV-2.

The serum, plasma, and PBMC-based analyses will be used to address scientific questions related to long COVID, such as the identification of prognostic biomarkers, understanding whether long COVID represents a single versus multiple unique pathologies, and associating biomarker profiles with patient-reported outcomes data. Analyses performed from banked samples may also be integrated with biomarker and other data from samples that were collected during the acute phase of SARS-CoV-2 infection. This will enable relationships between acute and long-term phases of COVID-19 to be explored, including better understanding the biology of COVID-19 over time,

and evaluating potential biomarkers during acute infection that may be predictive of casirivimab and imdevimab response during the long-term phase of disease.

Unused or residual samples may be retained as described in Section 9.2.8.

9.2.9.3. Monitoring for SARS-CoV-2 Reinfection

Patients in the long COVID sub-study will be asked to report any positive SARS-CoV-2 local test results obtained outside of the study, starting from the day at which they consent to the long COVID sub-study. Test results obtained prior to the date of consent will not be collected. Positive results will be reported as an AESI (Section 10.1.4).

Details regarding the positive SARS-CoV-2 local test result (eg, date of testing, specimen type, assay used) will be captured in the corresponding AESI data collection page.

9.2.9.4. Recording New Medical Diagnoses or Conditions

In the long COVID sub-study, any new medical condition(s) diagnosed after randomization (eg, newly diagnosed diabetes mellitus) will be captured and reported as an AESI, but will not require expedited reporting (Section 10.1.4).

Patients who previously consented to the sub-study but have already completed their end of study visit will be asked to consent to have this information collected.

Details regarding the new diagnoses or conditions (eg, preferred term [PT] for the diagnosis, date of diagnosis, and any other available information) will be captured in the corresponding AESI data collection page.

9.2.10. Pharmacogenomic Analysis (Optional)

Eligible patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of samples. When enrollment was open, newly-enrolled patients had blood samples collected for both DNA and RNA. Patients who are currently enrolled and subsequently consent to the sub-study will only have a blood collection for DNA. Patients who have already consented to this sub-study cannot consent a second time.

The blood sample for RNA must be collected pre-dose on day 1. Blood sample for DNA should be collected at the screening/baseline visit but may be collected at any visit.

The samples will be collected for pharmacogenomics analyses to understand the genetic and/or transcriptional determinants of efficacy and safety associated with the treatments in this study and the molecular basis of COVID-19 (and long COVID, as applicable). These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the Sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic and/or transcriptional associations with clinical or biomarker response to REGN10933+REGN10987, other COVID-19 clinical outcome measures and possible treatment-emergent SAEs and AESIs. In addition, associations between genomic variants and prognosis or progression of COVID-19 (and long

COVID, as applicable). may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic and transcriptional markers related to the study drug, target pathway, COVID-19, or long COVID.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

Results from the genomic and transcriptional analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

In this study, only targeted treatment-emergent AEs will be recorded:

- **All phases:** Treatment-emergent AESIs (grade ≥2 hypersensitivity and grade ≥2 IRRs; see Section 10.1.3)
- **All phases, including long COVID sub-study:** Treatment-emergent SAEs
- **Phase 1 only:** TEAEs (grade 3 or grade 4 only)
- **Long COVID sub-study only:** positive SARS-CoV-2 local test result, from the day of consent to sub-study until day 180
- **Long COVID sub-study only:** Any new medical condition that was diagnosed after randomization, until day 180

The investigator must promptly record treatment-emergent SAEs, treatment-emergent AESIs), and (in phase 1 only) grade 3 or 4 TEAEs occurring during the observation period (see Section 11.4.10.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as TEAE, provided that it fulfills the above criteria.

Throughout the study, the investigator will determine whether any treatment-emergent SAEs, treatment-emergent AESIs, and (in phase 1 only) grade 3 or 4 TEAEs have occurred by evaluating the patient. These events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all TEAEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on TEAEs (grade 3 or 4), treatment-

emergent SAEs, and treatment-emergent AESIs until they have resolved or are considered clinically stable.

Always report the diagnosis as the AE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance and whether they fulfil the criteria of TEAEs (grade 3 or 4), treatment-emergent SAEs, or treatment-emergent AESIs and will need to be reported. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as TEAEs if they fulfill reporting criteria for the study (ie, treatment-emergent SAE, treatment-emergent AESI, TEAE [grade 3 or 4]) or require corrective treatment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the informed consent form [ICF]) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any treatment-emergent SAE that may occur subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should also be reported.

All treatment-emergent SAEs, treatment-emergent AESIs, and pregnancies are to be reported according to the procedures in Section 10.1.3.

Note that patient-reported outcome (PRO) data (eg, patient-reported questionnaires, surveys, and instruments) are generally not reportable as individual AEs. However, if the investigator is made aware of any AE that (in his or her judgement) is related to study drug, the AE will be reported and recorded as described in Section 10.1.2.

10.1.2. Reporting Procedure

All treatment-emergent SAEs, treatment-emergent AESIs, and (in phase 1 only) treatment-emergent grade 3 or 4 AEs must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, relevant concomitant procedures, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE eCRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the Sponsor (or designee) within 24 hours of learning of the event:

- **Treatment-emergent SAEs**
- **Treatment-emergent AESIs** (serious and nonserious), defined as:
  - Grade ≥2 infusion-related reactions
  - Grade ≥2 hypersensitivity reactions
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient or female partner of a male study patient for up to 6 months after the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the Sponsor.

10.1.4. Other Adverse Events of Special Interest That Do Not Require Expedited Reporting to Sponsor

The following is considered an AESI and will require additional data collection (Section 9.2.9.4). However, these AESIs do not require expedited reporting to the Sponsor:

- **Long COVID sub-study only:** positive SARS-CoV-2 local test result
- **Long COVID sub-study only:** any new medical condition that was diagnosed after randomization

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).

- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an adverse event that had occurred in a more severe form, might have caused death.
- Requires in-patient **re-hospitalization** (readmission after discharge) or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new adverse event as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest for this study are defined in Section 10.1.3.

10.2.3.1. Infusion-Related Reactions and Hypersensitivity

Infusion-related reactions are defined as any relevant adverse events that occurs during the infusion or up to day 4.

Hypersensitivity reactions are defined as any relevant adverse event that occurs during the infusion or up to study day 29.

10.2.4. Severity

The severity of adverse events (including test findings classified as adverse events) will be graded using the current version of the NCI-CTCAE v5.0 (Division of Cancer Treatment and Diagnosis [DCTD], 2020). TEAEs that are evaluated as CTCAE grade 3 or 4 will be collected in addition to treatment-emergent SAEs and treatment-emergent AESIs as discussed above.

Treatment-emergent AEs, treatment-emergent SAEs, or treatment-emergent AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 5.

Table 5: NCI-CTCAE Severity Grading System for Adverse Events (v5.0)

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
† Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.5. Causality

The Investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The adverse event follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The adverse event follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.

- Not Related:
  - The adverse event does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The adverse event follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The adverse event does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the Sponsor in a timely fashion. The Sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board, Ethics Committee, and Investigators

During the study, the Sponsor and/or the CRO will inform health authorities, ECs/Institutional Review Board (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug, as appropriate per local reporting requirements. In addition, the Sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the Sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the Sponsor.

Event expectedness for study drug is assessed against the Reference Safety Information section of the Investigator's Brochure(s) that is effective for expedited safety reporting.

At the completion of the study, the Sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and ECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plans (SAPs) for the study. There will be separate SAPs for different portions of the study. The phase 1/2 SAP(s) specified the analysis for portions of phase 1 and phase 2 patients. The phase 1/2/3 SAP specifies the final efficacy and safety analyses for the remaining patients across all three study phases. The final SAPs will be issued before the first database lock in each portion of the study.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

Overview of the Final Statistical Analysis Plan

This final SAP outlines the strategy and statistical methods to be used in the final analysis of data from all phases and all cohorts in the prematurely terminated study COV-2066, as below:

Efficacy Analysis

The efficacy analysis will be performed for the modified full analysis set (mFAS, defined in Section 11.3) of the following pooled cohort of patients and individual subsidiary cohorts, representing the totality of patients in this prematurely terminated study who were not unblinded in the database lock on 22 December 2020. In this document, the prematurely terminated phase 3 cohort 1 is referred as phase 3 cohort 1 and prematurely terminated phase 2 cohort 1A as phase 2 cohort 1A.

- Pooled phase 3 cohort 1 and phase 2 cohort 1A
- Phase 3 cohort 1
- Phase 2 cohort 1A

In each of these data sets (ie, the 2 prematurely terminated cohorts and the pooled cohort), the analyses will be conducted in the mFAS for the following patient populations. The mFAS is defined as patients that have a positive central-lab confirmed SARS-CoV-2 RT-qPCR result from an NP swab sample and the efficacy analysis was conducted in the mFAS to ensure detectable virus was present at baseline.

- Seronegative mFAS
- High Viral Load mFAS, where high viral load is defined as $>10^6$ copies/mL at baseline
- Overall mFAS

The **primary** virologic endpoint is time-weighted average change from baseline viral load in nasopharyngeal (NP) samples through Day 7. The primary analysis will be performed in the Seronegative mFAS population that is combined across the 2.4 g and 8g doses and pooled across phase 3 cohort 1 and phase 2 cohort 1A.

The **primary** clinical endpoint is death or mechanical ventilation. It will be estimated based on the proportion of patients who died or went on mechanical ventilation from Day 6 through Day 29, where events occurring during the first 5 days will excluded because of the notion that clinical impact would occur only after achieving several days of viral suppression. This observation was noted in the analysis of data from phase 1/2 portion of this study. In addition, the endpoint of death or mechanical ventilation from Day 1 through Day 29 will also be evaluated. The primary analysis will be performed for the High Viral Load mFAS, Seronegative mFAS, and the Overall mFAS in the pooled phase 3 cohort 1 and phase 2 cohort 1A and combined across the 2.4 g and 8 g doses of REGN10933+REGN10987. To control alpha at a strict 0.05 level, the two primary endpoints will be tested hierarchically, with the virologic endpoint tested first.

Safety Analysis

The safety analysis will be performed for the following cohorts, separately. Patients in phase 1/2 cohort 1, phase 2 cohort 2 and cohort 3 are included into the analysis because more safety data were collected for the patients after the database lock on 22 December 2020.

- Phase 2 cohort 1A
- Phase 2 cohort 2
- Phase 2 cohort 3
- Phase 1/2/3 cohort 1 combined

Pharmacokinetics (PK) and Immunogenicity Analysis

The PK and ADA analysis will be performed for phase 1/2/3 cohort 1 combined, phase 2 cohort 1A, phase 2 cohort 2, and phase 2 cohort 3, separately. The NAb analysis will be performed for phase 2/3 patients.

11.1. Statistical Hypotheses

11.1.1. Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A)

The statistical hypotheses are presented in Table 6.

Table 6: Phase 3 Statistical Hypotheses

Type	Null Hypothesis
Primary virologic endpoint	There is no difference in the time weighted average change from baseline viral load in NP sample through day 7 between the REGN10933+REGN10987 2.4g and 8.0g **combined** dose group and placebo in the **Seronegative mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
Primary clinical endpoint	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 6 to day 29** in the **High Viral Load mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A

Type	Null Hypothesis
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 6 to day 29** in the **Seronegative mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 6 to day 29** in the **overall mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 1 to day 29** in the **High Viral Load mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 1 to day 29** in the **Seronegative mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A
	There is no risk reduction in the REGN10933+REGN10987 2.4g and 8.0g **combined** dose groups versus placebo in terms of cumulative incidence of death or mechanical ventilation **from day 1 to day 29** in the **overall mFAS population** in the pooled phase 3 cohort 1 and phase 2 cohort 1A

11.2. Justification of Sample Size

The initial sample size for this study was estimated separately for phase 1 and phase 2 (ie, prior to protocol amendment 6) and it was based on the original primary endpoint: virologic efficacy endpoint of time-weighted average change from baseline in viral load. The final estimates on sample size were based on assumptions related to the clinical endpoint of death or mechanical ventilation (see Section 11.2.3).

11.2.1. Phase 1 (Sentinel Safety Group; Cohort 1 only)

The sample size for phase 1 is a total of 60 patients randomized in a 1:1:1 allocation ratio to REGN10933+REGN10987 combination therapy 2.4 g IV, REGN10933+REGN10987 combination therapy 8.0 g IV, or placebo, ie, approximately 20 patients per arm across 3 treatment arms, stratified by the background standard-of-care. The sentinel safety group consists of the first 30 patients randomized in the combined phase 1 portions of R10933-10987-COV-2066 and R10933-10987-COV-2067.

Since one of the objectives of phase 1 is to assess safety and tolerability, the sample size will allow preliminary estimation of the incidences of SAE and AESIs in these investigational treatment arms relative to placebo.

The primary efficacy endpoint in phase 1 is the virologic endpoint of time-weighted average change from baseline in viral load (log_{10} copies/mL) in **NP swab samples** from day 1 to day 22.

Due to lack of data from the literature on the variation of time-weighted average change from baseline in viral load in COVID-19, the standard deviation of actual viral load values at a timepoint from the literature was used for the following calculation. Assuming standard deviation of 2.1 $\log_{10}$ copies/mL (Cao, 2020), a sample size of 20 patients per arm in phase 1 will have at least 80% power to detect a difference of 1.91 $\log_{10}$ copies/mL between the treatment arm and placebo group, using a two-sample t-test at a 2-sided significance of α=0.05. The smallest treatment difference is approximately 1.34 $\log_{10}$ copies/mL.

11.2.2. Phase 2 (Cohort 1A, Cohort 1, Cohort 2*, and Cohort 3*)

** Per IDMC recommendation first received on 30 October 2020, and reiterated through 19 February 2021, patient enrollment in cohort 2 and cohort 3 has been placed on hold.*

The sample size of phase 2 cohort 1A was adjusted to approximate 1000 patients based on clinical judgement without statistical justification. However, this target was not reached because the enrollment was prematurely terminated due to slow enrollment rate.

Phase 2 will evaluate the efficacy and safety of 2 doses of REGN10933+REGN10987 versus placebo within cohort 1A, cohort 1, cohort 2 and cohort 3, ie, phase 2 contains 3 treatment arms each across 4 cohorts. Randomization will be stratified according to Section 8.6.

Initial Estimation of Phase 2 Sample Size

The sample size for phase 2 was originally based on the primary virologic endpoint of time-weighted average change from baseline in viral load ($\log_{10}$ copies/mL) from day 1 to day 22, using a 2-sample t-test at a 2-sided significance of α=0.05.

Similar to phase 1, the standard deviation of actual viral load values at a timepoint from the literature was used for sample size calculation due to lack of corresponding data from the literature. Assuming a ~23% dropout rate (including missing data at baseline) and a standard deviation of 2.1 $\log_{10}$ copies/mL (Cao, 2020), a sample size of 130 patients per arm (ie, 100 patients per arm with available data) across 3 treatment arms within each of the 4 cohorts, ie, 390 patients per cohort (for a total of 1560 patients in the phase 2 portion of the study) will have 80% power to detect a difference of 0.84 $\log_{10}$ copies/mL between each treatment arm and placebo in a cohort. If a standard deviation of 3.8 $\log_{10}$ copies/mL is assumed (Wang, 2020b), the detectable difference at 80% power would be 1.51 $\log_{10}$ copies/mL.

Phase 1/2 Estimation of Sample Size

Per protocol amendment 6, statistical power calculations are provided for the cumulative incidence of death or mechanical ventilation for phase 1/2 cohort 1.

For phase 1/2 analysis in cohort 1, assuming a total number of events (death or mechanical ventilation) will be 35, that the cumulative incidence of death or mechanical ventilation in placebo is 25% at day 29 (placebo rate was 12.5% in Sponsor's Kevzara® [sarilumab] study 6R88-COV-2040 in COVID-19 hospitalized randomized and treated patients receiving low flow oxygen supplementation at baseline; further assume placebo rate is twice this in seronegative mFAS), and using a futility threshold of α=0.3 (1-sided), the minimum hazard ratio (HR) between REGN10933+REGN10987 dose group versus placebo that excludes futility is 0.827 (ie, minimum risk reduction 17.3%). If the observed risk reduction is approximately 17% or lower, the assessment of efficacy in cohort 1 as currently designed will be declared futile.

The alpha level for futility in this study is consistent with that used in the ACTIV-3 protocol for a similar cohort of patients with COVID-19 (NIAID, 2020).

For phase 1/2 key secondary analyses in cohort 1, and using assumptions about event rates as described above, about 43 total events in the seronegative mFAS will be needed to achieve 80% power to detect a risk reduction of 50% (HR=0.5) between any REGN-COV2 dose group versus placebo, at α=0.1 (one-sided) level of significance. Assuming patients are followed through day 29, and accrual takes 90 days, and assuming that 30% of FAS (randomized and treated) patients are in the seronegative mFAS, a total of approximately 250 randomized and treated patients across 3 arms will be needed in phase 1/2 in the three treatment groups.

Table 7: Statistical Power for Death or Mechanical Ventilation Endpoint: Phase 1/2 Cohort 1

α (Overall Type 1 error)	Power	Cumulative incidence of death or mechanical ventilation in Placebo by Day 29 (assumption)	Hazard Ratio	# of Events needed in seronegative mFAS	Total Sample Size estimated
0.1 (one-sided)	80%	25%	0.5	43	250
0.1 (one-sided)	80%	25%	0.6	78	413
0.1 (one-sided)	90%	25%	0.5	62	360
0.1 (one-sided)	90%	25%	0.6	114	604

11.2.3. Phase 3 (Cohort 1)

Initial estimation

The sample size for phase 3 was initially estimated to be 1350 patients (150 patients per arm across 3 treatment arms in 3 cohorts). Based on the new endpoint of death or mechanical ventilation, the sample size for phase 3 has been re-estimated to be 2505 patients in each of cohort 1 and cohort 1A.

The study was planned to continue enrolling additional patients seamlessly into the phase 3 portion of the study, until an adaptation decision on the dose(s), primary endpoint and final sample size for phase 3 is made based on the phase 2 data analysis. A total sample size of approximately 5010 patients was estimated for the phase 3 portion of the study (2505 per cohort, 835 per arm across 3 treatment arms in 2 cohorts). For cohort 1, a total of 241 events (estimated sample size of 2505 patients [835 patients per arm]) would have been needed to provide 90% power at α=0.05 (2-sided) using a log-rank test to detect a risk reduction of 35.8% (ie, HR=0.642) in the cumulative incidence of patients who died or went on mechanical ventilation, assuming a 12.5% cumulative incidence rate in the placebo group by day 29.

Final sample size

Finalization of the sample size and patient population for phase 3 was planned to be subject to change and would be determined after review of phase 2 data. However, enrollment of patients into the study was terminated prematurely by the Sponsor on 09 April 2021 because of extremely slow enrollment in the months preceding the decision. The sample size of phase 3 was not re-estimated.

Approximately 2252 patients were randomized in the study, which includes 60 patients in phase 1 cohort 1, 629 in phase 2 cohort 1, 755 in planned phase 3 cohort 1, 609 in phase 2 cohort 1A, 164 in phase 2 cohort 2 and 35 in phase 2 cohort 3.

Assuming the proportion of patients who died or went on mechanical ventilation from day 1 to day 29 in placebo group is 13.1% which is same as the blinded proportion in the Seronegative mFAS patients of the pooled phase 3 cohort 1 and phase 2 cohort 1A and alpha is 0.05 2-sided, the minimal significant difference in relative risk reduction between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group is 29.0%, 41.2%, and 36.6% for overall mFAS, Seronegative mFAS, and High Viral Load mFAS patients, respectively.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

Full Analysis Set (FAS): The full analysis set (FAS) includes all randomized patients who received at least one dose (full or partial) of the study drug. Analysis of the FAS population will be done according to the treatment allocated (as randomized).

Modified Full Analysis Set (mFAS): The modified full analysis set (mFAS) includes all FAS patients with a positive SARS-CoV-2 RT-qPCR conducted in the central laboratory in NP swab samples at randomization and analysis is based on the treatment allocated (as randomized).

Seronegative mFAS: The seronegative mFAS is defined as all patients in mFAS with documented seronegative status at the baseline.

High Viral Load mFAS: The High Viral Load mFAS is defined as all patients in mFAS with baseline viral load $>10^6$ copies/mL.

Both FAS and mFAS will be used for the summaries of demographic and baseline characteristics and analysis of clinical/biomarker endpoints. The mFAS will be used for the analysis of all efficacy endpoints, based on the principle that an anti-viral agent would only be anticipated to provide efficacy in patients with measurable virus at baseline. The seronegative mFAS as well as the high viral load mFAS will be used for the primary analysis and descriptive analysis of certain virologic endpoints and clinical endpoints. Additional analyses will be performed in the seropositive mFAS, as needed.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received a dose (full or partial) of the study drug. Analysis of the SAF will be done according to the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on day 1. Since the treatment of "as treated" is same as "as randomized" in this study, the FAS is equivalent to the SAF. Therefore, the treatment administration and all clinical safety variables will be analyzed using the FAS.

11.3.3. Pharmacokinetics Analysis Sets

The pharmacokinetics (PK) analysis population includes all patients who received any study drug of REGN10933 and REGN10987 and who had at least 1 non-missing drug concentration

measurement following the first dose of study drug as indicated in the Schedule of Events table. Patients will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all subjects who received any study drug (active or placebo) and at least one non-missing ADA result from the ADA assay after a first dose of the study drug or placebo.

The NAb analysis set (NAS) includes all treated subjects who received any study drug (active or placebo), have at least one non-missing ADA result following the first dose of study drug (active or placebo), and either tested negative at all ADA sampling times or tested positive for ADA with at least one non-missing NAb result after first dose of the study drug (active or placebo). Subjects who are ADA negative are set to negative in the NAb analysis set.

Subjects will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, Q1, median, Q3, standard deviation (SD), minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

11.4.1. Demography and Baseline Characteristics

Demographic and baseline characteristics variables will be summarized by treatment group, and all groups combined. These will be analyzed for FAS and mFAS populations. Similar analysis will be performed by baseline serostatus and baseline viral load categories (≤ 106 copies/mL and >106 copies/mL) for mFAS population.

11.4.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined in the mFAS and FAS population.

11.4.3. Prior / Concomitant Medications or Procedures

Prior or concomitant medications/procedures will be summarized by treatment groups. Summaries will present patient counts (and percentages) for all medications, dictionary coded by WHODRUG, by decreasing frequency of the overall group incidence (or high dose group incidence in tables where the overall is not presented) of ATC followed by ATC level 2, ATC level 4 and PT. Focus of the results will be on the list of targeted medications in the FAS and mFAS populations.

Number and proportion of patients undergoing a prior/concomitant procedure(s) will be summarized, sorted by decreasing frequency of SOC and PT based on the incidence in the overall group incidence (or high dose group incidence in tables where the overall is not presented). Patients will be counted only once for each SOC and PT linked to the procedure.

Prior or concomitant medications/procedures of interest for COVID-19 will be summarized similarly.

11.4.4. Patient Disposition

The following summaries will be provided for both mFAS and FAS populations.

- The total number of randomized patients: received a randomization number
- The total number of randomized patients who were not treated by study drug
- The total number of randomized patients who discontinued the study, and the reasons for discontinuation
- A summary of analysis sets including FAS, mFAS, SAF, PK, immunogenicity (ADA), and NAb analysis set (NAS)

11.4.5. Extent of Study Treatment Exposure

The following variables will be analyzed by treatment group:

- Duration of intravenous infusion
- Total volume of drug administered (units: mL)
- Number of patients with total planned dose administered (yes/no)
  - If no, reason for not administration of total planned dose (equipment failure, adverse event, other)
- Number of patients with infusion interruptions (ie, patients completed the full dose but had infusion interruptions)
- Number of patients with infusion discontinuation (ie, patients didn't completed the full dose infusion)

The number and percentage of patients randomized and exposed to double-blind study drug will be presented for each treatment group.

11.4.6. Efficacy Analyses

The efficacy analyses will be performed for the following patients on all efficacy endpoints, separately. The comparisons in all efficacy endpoints will be performed between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group as well as between each treatment group and placebo group.

- Pooled phase 3 cohort 1 and phase 2 cohort 1A patients
- Phase 3 cohort 1 patients (ie, patients randomized after 01 December 2020 in cohort 1)
- Phase 2 cohort 1A patients

11.4.6.1. Primary Efficacy Analyses

11.4.6.2. Analysis of Primary Virologic Efficacy Endpoint

The primary analysis on the comparison between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo with respect to the virologic endpoint of time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7 and other post-baseline visit timepoint will be performed in the Seronegative mFAS in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The estimand for the analysis is the difference in means between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Data collected after use of convalescent plasma therapy or other anti-spike monoclonals will be excluded from efficacy analysis. All other available data will be used in the analysis regardless of intercurrent events such as rescue medication or discontinuation, ie, treatment policy approach.

The analysis will be based on the observed data with no imputation for missing data except as defined in the SAP for viral load values that are below lower limit of detection (<LLOD), below lower limit of quantification (<LLOQ) or above upper limit of quantification (>ULOQ) of the assay.

The variable will be analyzed using the Analysis of Covariance (ANCOVA) model with treatment group and the type of background standard-of-care as fixed effects, and baseline viral load and treatment by baseline interaction as covariates.

The least squares means estimates for time-weighted average daily change from baseline in viral load for each treatment group, as well as the difference between the REGN10933+REGN10987 2.4g and 8.0g combined doses and placebo as well as between each individual dose treatment group and placebo, will be provided along with the corresponding two-sided p-value, standard error, and associated 95% confidence interval.

11.4.6.3. Analysis of Primary Clinical Efficacy Endpoints

The primary efficacy analysis will be the comparison between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The primary clinical endpoint defined in Section 4.1 will be analyzed using the landmark analysis approach for day 6 through day 29, as well as analyzed for day 1 through day 29 in the order specified in Section 11.4.9.

The proportion of patients who died or went on mechanical ventilation will be analyzed using either the exact method for binomial distribution or asymptotic normal approximation method. If the number of events is small (eg, $np \leq 5$ or $n(1-p) \leq 5$ in any treatment group, where n is the number of patients in the treatment group and p is the proportion of events), then the Fisher's exact test will be applied. Otherwise, stratified Cochran-Mantel Haenszel (CMH) test, stratified by the type of background standard-of-care (antiviral therapies and non-antiviral therapies), will be applied. Relative risk and relative risk reduction and corresponding 95% confidence intervals compared to placebo group will be estimated by Farrington-Manning method. Missing data will be considered as non-events.

The analysis will be performed for the High Viral Load mFAS, the Seronegative mFAS, and the overall mFAS.

11.4.7. Descriptive Analysis of Secondary Efficacy Endpoints

All analyses for the secondary efficacy endpoints are descriptive and all p-values are nominal. Details are provided in the SAP.

11.4.8. Exploratory Analysis

Exploratory analyses related to long COVID will be summarized descriptively. Additional details will be provided in a separate long COVID statistical analysis plan (SAP) from the study SAP. This SAP may also describe additional analyses of symptoms and/or biomarkers.

11.4.9. Control of Multiplicity

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary virologic and clinical outcome endpoints in comparison between the combined doses of REGN10933+REGN10987 treatment group and placebo group in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level.

The hierarchy is provided in Table 8.

Table 8: Hierarchical Testing Order

Type	Description	Testing Order
Primary virologic outcome	Time-weighted average change from baseline viral load in NP sample through day 7 **in seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	1
Primary clinical outcome	Proportion of patients who died or went on mechanical ventilation **from day 6 to day 29 in High Viral Load mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	2
	Proportion of patients who died or went on mechanical ventilation **from day 6 to day 29 in Seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	3
	Proportion of patients who died or went on mechanical ventilation **from day 6 to day 29 in overall mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	4
	Proportion of patients who died or went on mechanical ventilation **from day 1 to day 29 in High Viral Load mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	5
	Proportion of patients who died or went on mechanical ventilation **from day 1 to day 29 in Seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	6
	Proportion of patients who died or went on mechanical ventilation **from day 1 to day 29 in overall mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo	7

11.4.10. Safety Analysis

The analysis of safety data will be performed for cohort 1 in combined phases 1, 2 and 3, and phase 2 cohorts 1A, 2 and 3, separately in the FAS population.

In this study, only targeted treatment-emergent adverse events (as defined in Section 10.1.1) will be recorded.

The safety analysis will be based on the reported SAEs and AESIs and other safety information (clinical laboratory evaluations and vital signs).

The summary of safety results will be presented for each treatment group.

11.4.10.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the study drug administration.
- The observation period is defined as the time of study drug administration to the last study visit.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period.

Analysis

The verbatim text, the PT, and the primary system organ class (SOC) will be listed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

All adverse events reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The PT, and the primary system organ class (SOC) will be listed.

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

An overview of adverse events will be provided by treatment group and for combined dose groups of R10933+R10987, including:

- Total number of TEAEs, SAEs, Total number of AESIs, Serious AESIs, Grade 3 or 4 TEAEs, as well as
- The number and percentage of patients with any TEAE, any SAE, any AESI, any serious AESI, any grade 3 or grade 4 TEAE, any fatal TEAEs, any TEAEs leading to withdrawal from the study, any TEAEs leading to study infusion discontinuation, and any TEAEs leading to study infusion interruption.

Summaries of SAEs and AESIs by treatment group and for combined R10933+R10987 doses will include number (n) and percentage (%) of patients with at least:

- Treatment-emergent AE by SOC and PT

- Treatment-emergent AE by SOC and PT and CTCAE grade
- Treatment-emergent AE related to study treatment by SOC and PT
- Treatment-emergent SAE by SOC and PT
- Treatment-emergent AESIs presented by SOC and PT
- Treatment-emergent grade 3 or 4 AEs presented by SOC and PT

Counts will be provided according to treatment group for each PT within each SOC. Percentages will be calculated using the number of patients from the FAS in each treatment group.

Primary SOCs will be sorted according to decreasing order of frequency in combined treatment group. Within each primary SOC, PTs will be sorted by decreasing frequency in combined treatment group.

11.4.10.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, SpO_2, FiO_2, and respiration rate) will be summarized using descriptive statistics. Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized.

Laboratory Tests

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

11.4.10.3. Treatment Exposure

Exposure to study drug will be examined for each patient. The total number of doses administered to each patient and exposure related parameters (eg, duration of IV infusion, total volume of drug administered, etc) will be analyzed and summarized using descriptive statistics by treatment arm in the SAF.

11.4.10.4. Treatment Compliance

Treatment compliance in terms of total dose and infusion interruption will be summarized. The analysis methods will be detailed in the SAP.

11.4.11. Pharmacokinetics

11.4.11.1. Analysis of Drug Concentration Data

Concentrations of REGN10933 and REGN10987 over time will be summarized by descriptive statistics for each treatment group. No formal statistical hypothesis testing will be performed.

11.4.11.2. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

At a minimum the viral-exposure response analysis will be performed.

11.4.12. Analysis of Immunogenicity Data

Immunogenicity variables will be summarized using descriptive statistics.

Immunogenicity will be characterized by the ADA responses and titers observed in subjects in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response (only applicable to phase 1) – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assays at all time points) by treatment arms
- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment arms and ADA titer categories

- Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects
- Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects
- Number (n) and percent (%) of transient treatment-emergent ADA positive subjects

Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment groups and ADA titer categories

- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment arms and ADA titer categories

Listing of all ADA titer levels will be provided for subjects with pre-existing, treatment-emergent and treatment-boosted ADA response.

11.4.12.1. Analysis of Neutralizing Antibody Data

The absolute occurrence (n) and percent of subjects (%) with NAb status in the NAb analysis set will be provided by treatment groups.

11.4.13. Analysis of Pharmacodynamic and Exploratory Biomarker Data

The concentrations of exploratory PD/Biomarkers over time will be summarized using descriptive statistics and may be reported separately from the CSR.

11.5. Interim Analysis

No interim analyses are planned.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and Sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the Sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, SAEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The eCRF data for this study will be collected with an electronic data capture (EDC) Medidata Rave.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk based approach to study monitoring and oversight, aligned with risk based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends.

The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and eCRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the eCRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required eCRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient eCRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the Sponsor regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the Sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the Sponsor’s participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Sponsor immediately
- Taking all appropriate measures requested by the Sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the Sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of eCRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the Sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the Sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the Sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

An informed consent form (ICF) can be defined as either a paper consent form or an electronically-delivered consent (eConsent). An eConsent may be provided only where allowable by local laws and regulations and by site policies.

Due to disease severity, quarantine restrictions and/or other reasons related to COVID-19, it may be necessary to implement temporary or alternative measures to obtain informed consent per procedures outlined in the investigator site file.

The ICF used by the investigator must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the Sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in

language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on eCRFs or other documents submitted to the Sponsor. Documents that will not be submitted to the Sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the Sponsor database, will be treated in compliance with all applicable laws and regulations. The Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the Sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The Sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The Sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the Sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Closeout of a Site

The Sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

The investigator must notify the Sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The Sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A MASTER PROTOCOL ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-CoV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF HOSPITALIZED PATIENTS WITH COVID-19 and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the Sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Hospitalized Patients with COVID-19

Protocol Number: R10933-10987-COV-2066

Protocol Version: Amendment 9 US

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

APPENDIX A. Oxygenation Equivalence for Eligibility

Sites located in high-altitude areas (>1500 m above sea level) should use Table 9 to get the appropriate high-altitude equivalents for sea-level oxygenation measurements.

Table 9: High Altitude Equivalents for Sea-Level Oxygenation Measurements

Eligibility Criterion	Protocol-Defined Threshold (Sea-Level Measurement)	High-Altitude Equivalent For Eligibility
Inclusion criterion 5b	O_2 saturation >93%	O_2 saturation >90%
Inclusion criterion 5c	SpO_2 ≤96%	SpO_2 ≤93%
Exclusion criterion 1 ***(Phase 1 only)***	O_2 saturation >94%	O_2 saturation >91%

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